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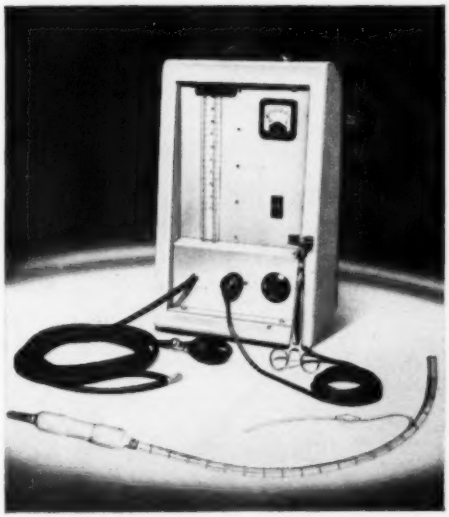

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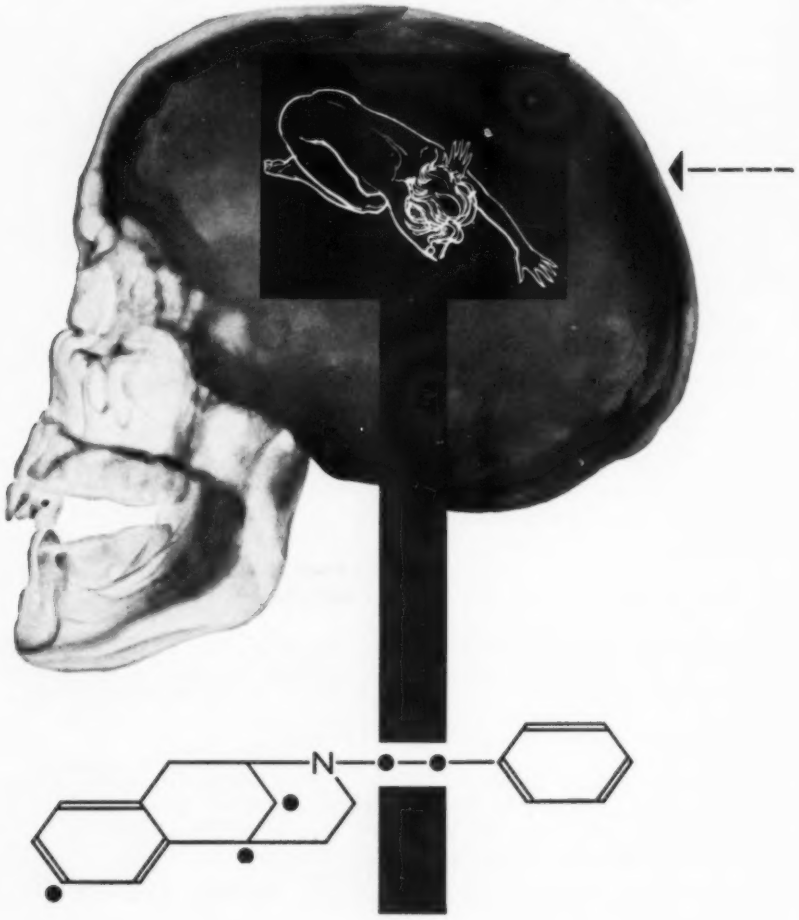

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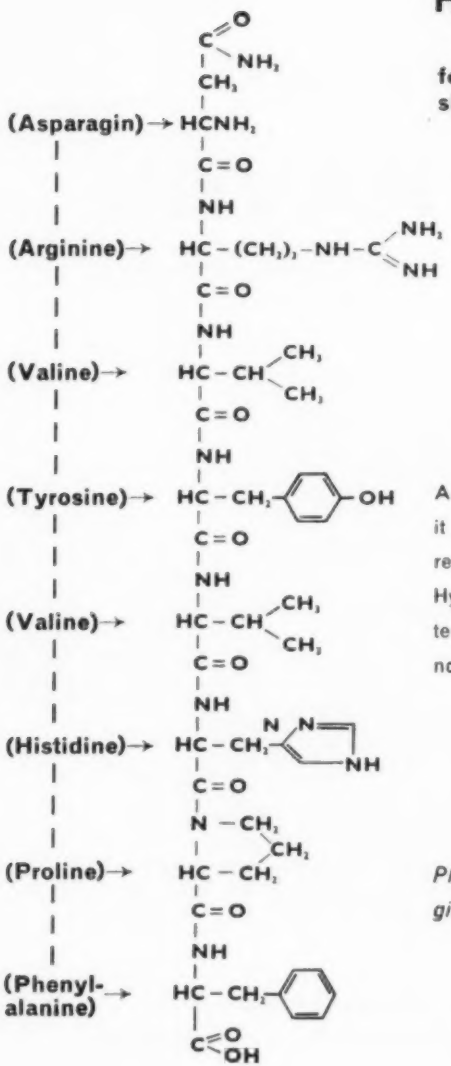

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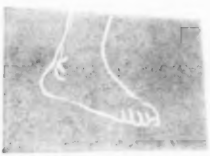

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ANNALS OF
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CONTENTS

APRIL 1960

Telegrams: Collsurg, Holb, London
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RECENT ADVANCES IN THE SURGERY OF TYPHOID FEVER

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

17th November 1959

by

R. L. Huckstep, M.A., M.D. (Cantab.), F.R.C.S. (Eng.), F.R.C.S. (Ed.)
Lecturer in Surgery, University of East Africa

" One man in his time plays many parts "

THIS QUOTATION FROM Shakespeare's " Seven Ages of Man " can aptly be used to describe the diverse and varied ways in which typhoid fever, the King of Actors on the Stage of Disease, can present and progress. There are very few conditions which cannot be mimicked in this, the most lethal of all enteric diseases, and the surgical complications are as varied and as numerous as the medical. A case of typhoid may present as a case of apparent appendicitis, progress to an acute intestinal haemorrhage, simulate an acute meningitis, cause an " acute abdomen " with perforation, and finally in convalescence, with its evil spent, linger on as an orchitis, a chronic cholecystitis, or an osteomyelitis.

Typhoid has been recognized for many centuries. Hippocrates described a fever which was probably typhoid. It is said that Antonius Musa, a Roman physician, became famous by treating the Emperor Augustus with cold baths when he fell ill with typhoid. In 1684, Thomas Willis gave a fairly accurate description of typhoid in his famous *Practice of Physick*, but the standard triad of treatment in those days of " let blood, vomit and purge " might leave much to be desired! In the days of John Hunter (Fig. 1) in the eighteenth century, typhoid was a very real and lethal disease in this country. In the Hunterian Museum there are no fewer than 13 of John Hunter's specimens showing typhoid involvement of gut.

Typhoid is no respecter of classes, and both Prince and Commoner are susceptible to its virulence. Prince Albert, the Prince Consort, died of it in 1862, and it has been said that there were 50,000 cases a year in England alone at about this time. This has certainly changed for the better, but the number of typhoid cases has never fallen, even in recent years, below a hundred a year in England, with sporadic larger outbreaks, and in the 10 years between 1947 and 1957 there were 2,099 notified cases in England and Wales.

In many countries, however, typhoid is still an everyday problem. For instance, 19,551 cases were notified in Italy in 1955 (Table I), and well over 40,000 in the North and South American Continents. In 1951, 81,575 cases were notified in South Korea with 14,051 deaths, an indication

of the vast typhoid epidemics still occurring, particularly among the countless millions of the East. The reasons for this are not far to seek. Sanitation and hygiene are still abysmally poor in many of the lesser educated communities, and carriers are still numerous in many parts of the world. There were no less than 542 registered carriers in West Berlin alone in 1955.

War produces conditions ideal for typhoid outbreaks, as was shown in Korea; but in peace time English people are increasingly travelling by air to and from the more distant endemic areas of Africa and the East, and

Fig. 1. John Hunter—as a young man—by his brother-in-law Home.

are taking holidays in nearer places such as Spain and Italy. An appreciable number are returning with undiagnosed salmonellae infections including typhoid (Macrae, 1959).

The last Hunterian lecture on typhoid fever was delivered by Lord Webb-Johnson (Fig. 2) in 1917. This was a brilliant review of the cases dealt with in a military hospital in France, and described the advances in treatment known in the First World War. During the last decade, however, more progress has been made in the treatment of typhoid than

since John Hunter's day; firstly with the introduction of chloromycetin in 1948 (and its synthesis as chloramphenicol), and secondly a greater realization of the importance of the fluid and electrolyte balance as emphasized by H. L. Marriott in 1947. In addition, there have been many advances in diagnosis, prophylaxis and treatment. For these reasons, a restatement of the surgical diagnosis and treatment of typhoid fever from the surgical point of view would appear to be timely.

Fig. 2. Lord Webb-Johnson.

This paper is based on well over 1,000 cases of typhoid fever seen and treated personally in Kenya during the period February 1954 to May 1955. Of these 975 have been documented (Table II), 240 being investigated in considerable detail under clinical research conditions. The main findings will be based on these 240 " research " cases, amplified in places by experience with the other 735 patients. The material formed the basis of a Thesis in 1957 (Huckstep).

TABLE I

EPIDEMIOLOGY OF TYPHOID FEVER
Number of notified cases in 1955

Great Britain 221

Europe	Italy	19,551	*Asia*	Turkey	7,629
	Spain	14,394		Indonesia	6,081
America	United States	1,704	*Africa*	South Africa	3,997
	Colombia	14,561		Egypt	14,835

Carriers
(Registered in 1955)
West Berlin 542 chronic carriers

Epidemics in War
(Notified cases in 1951)
South Korea 81,575 cases with 14,051 deaths

TABLE II

TYPHOID FEVER — DIAGNOSTIC CRITERIA
Personal Series of 1,300 patients (approx.)

975 Documented

240 Patients (Clinical Research Series)		735 Patients (Subsidiary Series)
Strong Clinical Evidence		Laboratory, Circumstantial, or Clinical Evidence in all 735
Plus		*Plus*
Blood Culture ..	132	
Stool Culture ..	46	
Abscess Culture ..	2	Positive Bacteriological Evidence in a cross-section of 216 out of 735 Patients
Post Mortem Culture	2	
Widal T.O. over 1/480	58	
TOTAL	240 Pts.	

TABLE III

MAIN SYMPTOMS ON ADMISSION
(975 Patients)

	Research (240 Pts.)	Subsidiary (735 Pts.)	Total (975 Pts.)
Headache	179	552	731 (74.9%)
Abdominal Pain ..	168	424	592 (60.7%)
Joint Pains	105	422	527 (54.0%)
Diarrhoea *without* blood	88	201	289 (29.6%)
Severe Sore Throat ..	15	52	67 (6.9%)

SURGICAL DIAGNOSIS

The surgeon who is called upon to assess and treat an abdominal catastrophe in a patient who may be suffering from typhoid is confronted by a diagnostic necessity of major importance. The classical diagnostic tests, the Widal and blood culture, are of limited value because:

(1) They take too long.

(2) The Widal may be negative and the patient still have typhoid. Conversely, with large-scale T.A.B. inoculations a small rise in the Widal may occur in non-typhoid cases.

(3) Within 2 hours of chloramphenicol administration the blood is usually sterilized so that a newer method of treatment may invalidate an established diagnostic test.

(4) Stool culture has the disadvantage that it is usually not positive until the third week of illness, if then.

The surgeon must, therefore, have recourse to other diagnostic criteria:

(*a*) *History*

The history of contact together with an onset of low-grade fever are of special importance. The important symptoms on admission are shown in Table III.

(*b*) *Examination*

Abdominal tenderness (usually slight and lower), bronchitis, toxicity and mental confusion were found to be signs of especial diagnostic value (Table IV).

TABLE IV

MAIN SIGNS ON ADMISSION

(240 Patients)

Abdominal Tenderness (Mainly Slight) ..	60.8%
Bronchitis	55.8%
Toxicity	54.2%
Coated Tongue	39.2%
Abdominal Guarding (Mainly Slight) ..	25.0%
Palpable *and* Tender Spleen	13.9%

Two other signs of importance are a strange musty odour and an apathetic expression, the latter being helpful in differentiating the typhoid patient from one suffering from lobar pneumonia, malaria or bacillary dysentery. Nelson and Pijper (1951), among others, state that the rose spot of typhoid cannot be seen in a black skin, but it is in fact often visible and made more obvious by the application of a little oil to the skin. Figure 3 shows a biopsy of a rose spot, from a black patient.

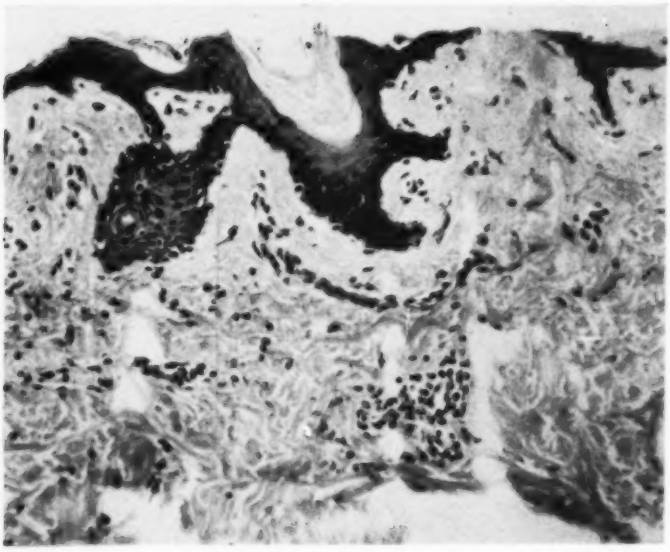

Fig. 3. Biopsy of a " Rose Spot " from a black patient (showing heavy melanin pigmentation, round cell infiltration and large vascular spaces).

(*c*) *Diazo reaction of urine*

This I believe to be the greatest single surgical diagnostic aid, and it can be done in 30 seconds under any conditions. Ehrlich described the test in 1883, and others at that time found it of great value. Few, however, in the last 40 years appear to have used it. With slight modifications it was used in 638 cases of typhoid and 2,115 controls. Others working in East Africa have confirmed its great usefulness (Manson-Bahr, 1958).

The diazo reagent is made up from 2 solutions, A and B (Fig. 4).

Solution A: Sulphanilic acid 0.5 G., concentrated hydrochloric acid 5.0 ml., distilled water 100 ml.

Solution B: Sodium nitrite 0.5 G., distilled water 100 ml.

40 parts of solution A are mixed with 1 part of solution B to make the diazo reagent, which will keep fresh in a refrigerator for 3 days. 5 ml. of diazo reagent are added to an equal quantity of the urine, a few drops of 30 per cent. ammonia are added, and the whole shaken up in a test tube. The colour of the froth alone is noted, a pink or red coloration being a positive reaction, and all other coloration considered negative.

The reaction is positive in many typhoid cases at some period between the 5th and 14th day of the illness, in relapses, and often at other times as well. It is occasionally positive in advanced tuberculosis, bacillary dysentery, and lobar pneumonia, but usually only weakly so. It is rarely positive in other conditions.

An early morning specimen of urine should be tested where possible because of its higher concentration. If the test is negative on one specimen it should be repeated on further specimens. Although the diazo solution should be made up fresh, typhoid urine weeks old will still give a positive reaction.

The results of the diazo reaction are shown in Table V. The salient points are:

(1) 79.4 per cent. of the typhoid patients in the research series had positive diazo reactions on admission.

(2) Out of a total of 638 typhoid patients tested, 82.9 per cent. had positive diazo reactions, and if only those tested between the 5th to the 14th day are included the percentage with a positive reaction is 90.6 per cent.

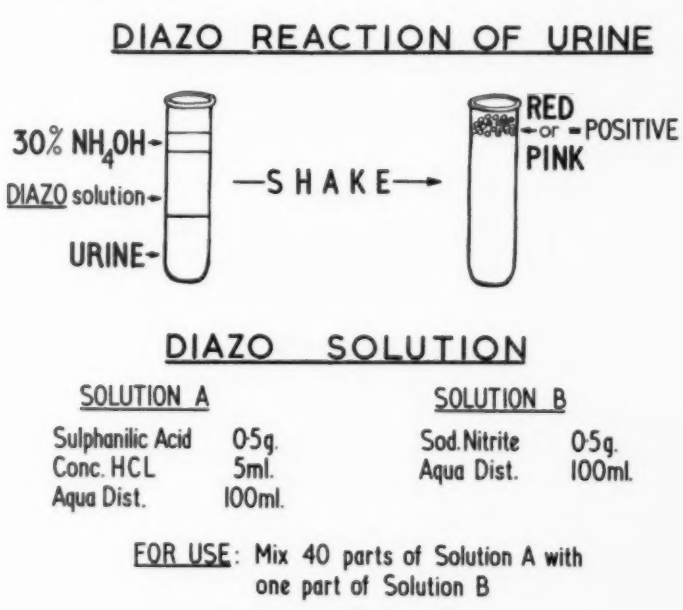

Fig. 4. Diazo reaction of urine.

TABLE V

RESULTS OF DIAZO TEST OF URINE

638 Typhoid Patients

	Positives
1. On Admission	79.4%
2. Irrespective when tested	82.9%
3. 5th to 14th days of illness only ..	90.6%

2,115 Control Patients
(107 different Medical and Surgical Conditions)

Mainly *Weakly* Positive	5.7%

In contrast to this only 5.7 per cent of the 2,115 patients in a control series had positive diazo reactions and these usually only weakly so. The control series included 107 different medical and surgical conditions.

Considerable research was done on the nature of the substance causing the positive diazo reaction and this has been published elsewhere (Huckstep, 1957).

Suffice it to say that, used correctly, and with due respect to its limitations, the diazo reaction of urine should be a major asset to the surgeon, especially where a complication such as intestinal perforation may obscure the diagnosis.

(*d*) *Other diagnostic tests*

The bone marrow, unlike the blood, is not sterilized within 2 hours by chloramphenicol, but one still has to wait 2 days for the result of culture.

A Widal in the value of O. antigen agglutination of 1/240 or over is practically diagnostic of typhoid, especially in the presence of other evidence. The H. antigen agglutination is much less specific.

The white blood count is of value in the differential diagnosis in so far as a count of over 10,000 is strong evidence against the diagnosis of typhoid. It should be made a routine test in all cases.

VALUE OF T.A.B.

In one epidemic in an isolated community of 17,000 in Kenya, there were 870 probable cases of typhoid with a high mortality and complication rate. Over 90 per cent. of these had received inoculations with alcoholized T.A.B. 3 or 4 months previously.

Marmion (1952, 1953) described two epidemics in Egypt involving 535 Royal Air Force personnel. Practically every one of these had had T.A.B. in recognized doses, and yet there was an appreciable morbidity, mortality and complication rate.

Anderson and Richards (1948) described a similar state of affairs in the Middle East with 110 cases of typhoid, 91 per cent. of whom had had T.A.B.

These findings are in contradiction to those of earlier workers. I feel, therefore, that improved sanitation and hygiene are more important factors in prophylaxis than T.A.B. itself. The answer to this important question may be to give a living attenuated vaccine of several phage types, but more research requires to be done on the subject.

GENERAL TREATMENT OF TYPHOID

Chloramphenicol is the drug of choice, and should always be given to all but the mildest cases. In this series it reduced the average duration of pyrexia from 14.6 to 4.1 days (Table VI).

TABLE VI

AVERAGE DURATION OF PYREXIA

Without Specific Chemotherapy	14.6 days
With Chloramphenicol and Aureomycin ..	4.6 days
With Chloramphenicol alone	4.1 days

The optimum chemotherapeutic treatment of typhoid fever is shown (Table VII). Salient points are:

(1) It must be given in adequate doses to the toxic patient despite the risk of aplastic anaemia and the toxic crisis. Both of these in my opinion have been over-rated.

(2) Dosage must be continued for at least 14 days, otherwise the relapse rate is markedly increased. T.A.B. may decrease the likelihood of a relapse.

(3) Cortisone is said to have an effect in the very toxic case, although I have not had personal experience of this in typhoid. There is an increased likelihood of perforation and haemorrhage with its use.

TABLE VII

GENERAL TREATMENT OF TYPHOID FEVER (CHEMOTHERAPY)

1. The Acute Fulminating or Severe Toxic Case
   1 G. Chloramphenicol 6 hourly for 3 days,
   then 0.5 G. Chloramphenicol 6 hourly for 12 days

2. The Ordinary Acute or Subacute Case
   0.5 G. Aureomycin } 6 hourly for 3 days,
   0.5 G. Chloramphenicol }
   then 0.25 G. Aureomycin } 6 hourly for 12 days
   0.25 G. Chloramphenicol }

3. Additional Treatment
   (a) Cortisone for the first 3 days in very severe toxicity, and in haemolytic anaemia, but *not* in abdominal complications.
   (b) Up to 4 G. stat. of chloramphenicol in extreme toxicity.
   (c) T.A.B. 0.5 ml. on the third afebrile day (uncomplicated cases).

Although treatment with a specific antibiotic has been mentioned first, the general care of the typhoid patient is still of foremost importance, although even this has changed recently. Strict confinement to bed is still important, because of the toxic effects on the myocardium. The absolute immobility which used to be advocated must, however, be tempered with physiotherapy in order to diminish the likelihood of complications such as bed sores, bronchopneumonia and venous thromboses. The patient's ambulation must be gradual, because myocardial damage may last for several weeks after the pyrexia has settled, quite apart from the risk of late complications and relapses.

The diet must be low in roughage because of the danger of intestinal perforation and haemorrhage. Except in cases of intestinal complications, however, there must be an adequate calorific intake, especially of protein, at all stages of the disease. The gastric diets I—IV are a good guide, using milk fortified with added protein and vitamins, especially ascorbic acid and iron.

Fluid and electrolyte balance is important as dehydration is common, and may occur rapidly. If an adequate fluid intake cannot be taken by mouth, the intravenous route is normally the method of choice in adults. In more primitive parts of the world, however, intravenous therapy may be impossible, and fluid may be given intraperitoneally. This will be discussed later.

Despite the optimum treatment of typhoid, however, complications are still common, relapses and carriers still occur, and there is an appreciable mortality. With a few exceptions, most reported mortality rates exceed 5 per cent. even with chloramphenicol. This is especially so abroad, where patients are likely to attend hospital much later, and the mild cases are usually never even seen by a doctor. Patients in Africa and the East also tend to be in a much poorer state of health, and are sometimes infected with massive doses of the typhoid bacillus. The overall mortality in the research series, i.e. mainly the more seriously ill patients and those with complications, was 5.4 per cent.

Two final points on general treatment should be considered:

Firstly, complications such as intestinal haemorrhage, perforation and orchitis may occur during convalescence, and a careful watch must, therefore, be kept.

Secondly, the carrier state, either urinary or faecal, is always a potential danger, and no patient should be sent home until six negative stool and urine cultures have been obtained.

SURGICAL COMPLICATIONS

Diagnosis of the acute abdomen in the typhoid patient

It is important not to subject typhoid patients to unnecessary operations for many reasons. They stand anaesthesia extremely badly, because of toxic effects on the liver and general poor state of myocardium and respiratory system; and although many abdominal catastrophes can be mimicked by typhoid fever, conditions such as cholecystitis and perforation are usually best treated conservatively.

The diagnosis of the acute abdomen in such patients is made difficult because:

(1) They are toxic and have a higher threshold to pain.

(2) The natural abdominal tenderness and sometimes guarding seen in these patients may mimic a true appendicitis.

(3) A toxic hepatitis and occasionally a haemolytic jaundice may occur in typhoid, and add to the difficulties in diagnosis of acute cholecystitis.

(4) Typhoid perforation of the intestine may be insidious, particularly when patients are on chloramphenicol, and often so if they are exhausted, toxic and delirious. Rapid deterioration in general condition, a rising pulse rate, paralytic ileus, and free fluid in the abdomen, may be the first indications of perforated gut.

THE TREATMENT OF TYPHOID PERFORATION

To appreciate the rationale of the treatment it is important to consider the pathology of perforations in some detail. In typhoid fever, the part of the gut to perforate is the lower ileum in most cases, because here there is an accumulation of Peyer's patches, and the disease selectively affects these lymphoid aggregations. John Hunter realized this, and 2 out of the 13 specimens in the Hunterian Museum are illustrated in Figures 5 and 6.

Figure 5 shows several enlarged and friable Peyer's patches in the lower ileum.

Figure 6 shows no obvious perforation, yet the gut in the lower ileum is paper thin in many places and liable at any moment to perforate at more than one spot. It can readily be appreciated that the repair of such a friable gut would be an almost impossible task, and attempts to suture it merely result in further tears. It may be likened to wet blotting paper, and on two occasions I have watched adherent lower bowel torn as the peritoneum was opened.

It may thus be seen that the danger lies in the perforation, not of one Peyer's patch, but of many; and that even where the gut does not perforate

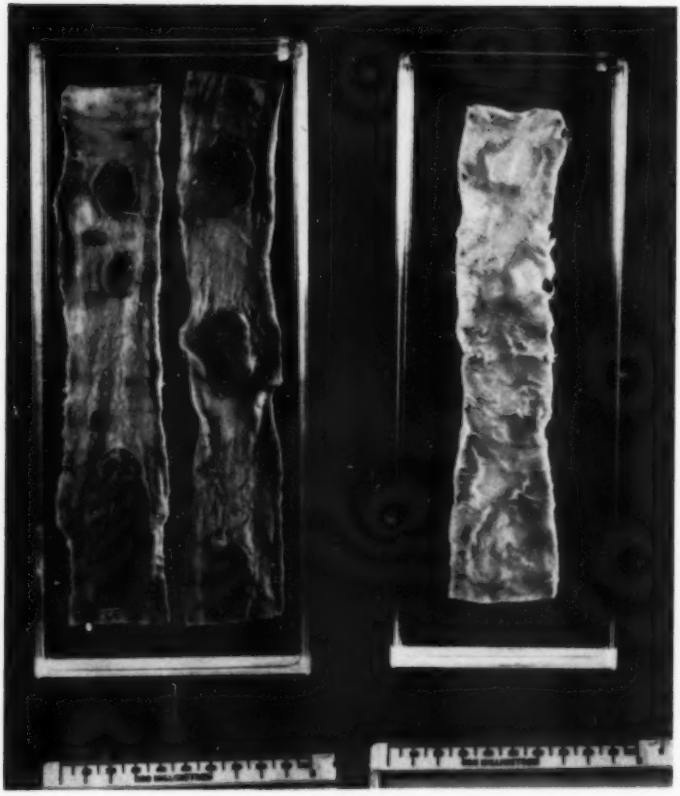

Fig. 5 (left). Hunterian specimen—showing several enlarged and friable Peyer's patches in the lower ileum.

Fig. 6 (right). Hunterian specimen—showing several large paper thin areas in the lower ileum, which are liable to perforation at more than one spot.

it tends to be friable. Such diffuse inflammation will also tend to make adjacent loops become adherent. One has the impression that this happens more often after chloramphenicol, because of a virtually sterile and presumably lower grade of perforation.

Despite the many dangers practically all authorities have hitherto advocated operative treatment. The results usually have been disastrous and reported mortalities very high (Table VIII). Webb-Johnson reported

TABLE VIII

TYPHOID PERFORATION—OPERATIVE AND CONSERVATIVE TREATMENT

Operative Treatment

	Mortality
Webb-Johnson (1917)	100%
Hamilton Bailey (1958)	Over 80%

Conservative Treatment

		Mortality	
Present Series (1954/45)	13 Pts. with Perforation	30%	20%
	7 Pts. with Peritonitis	0%	

a mortality of 100 per cent. in 1917, and Hamilton Bailey in 1958 (10 years after the introduction of chloramphenicol) well over 80 per cent. of deaths following operative intervention.

One case I operated on required a transverse colostomy because of pelvic obstruction, and after a stormy convalescence eventually recovered. The post mortem appearances in fatal cases of perforation, and loss of patients after operation, make me feel that an adequate operation is often impossible. I, therefore, decided to treat a series of patients by conservative measures only.

In my series treated conservatively there were 20 cases. 13 of these were diagnosed as intestinal perforation on several criteria, and this diagnosis was confirmed at post-mortem on those who died. A further 7 who had free fluid and other signs of peritonitis were labelled merely as " peritonitis ", although they were almost certainly cases of true, though atypical, perforation. 4 out of 13 of the cases of intestinal perforation died, and none out of 7 of the cases of " peritonitis ". This gave a mortality of 30 per cent. or of 20 per cent. if all 20 cases are included.

The method of treatment was by general methods similar to the Ochsner-Sherren regime plus large doses of chloramphenicol. Phenobarbitone gr. ½ t.d.s. after gastric aspiration was found useful in allaying vomiting. Very careful fluid and electrolyte replacement by intravenous routes was important, as there was on the one hand a toxic myocardium and on the other a dehydrated patient. Chloramphenicol was given in a dosage of 2 Grams 4-hourly in an adult for 2-3 doses, and then reduced to 1 Gram 4-hourly, gradually reducing the dose to 0.5 Gram 6-hourly as the patient improved. The danger of the so-called toxic crisis after large doses of chloramphenicol in typhoid is much over-rated. Oral administration of chloramphenicol is usually satisfactory, but the intravenous route may be better suited in some cases. Even if this route is preferred, some of the drug should be continued by mouth to make sure of the sterility of the bowel.

The exceptions to the rule of conservative treatment of perforation are:

(1) Sudden perforation in the otherwise convalescent patient. If this case is seen within 6 hours, I feel operation is the treatment of choice.

(2) The perforation leading to complications such as adhesions causing obstruction. One case of obstruction due to a pelvic abscess following perforation, and necessitating a transverse colostomy and drainage of the peritoneum, has been already mentioned.

Summarizing then, all perforations in typhoid fever, with these exceptions, should be treated conservatively, with large doses of chloramphenicol, and an Ochsner-Sherren regime. The high mortality of operative measures should, therefore, be drastically reduced, although not eliminated.

INTESTINAL HAEMORRHAGE

This is still a severe complication of typhoid fever (Table IX), and may occur despite chloramphenicol therapy. Its mortality rate has been greatly diminished by adequate and early blood transfusion. This complication, however, may sometimes be " silent ", and the first evidence of haemorrhage a collapsed patient with extreme pallor of the conjunctivae.

TABLE IX

ABDOMINAL COMPLICATIONS OF TYPHOID FEVER

	No. of Patients	*Mortality*
Intestinal Perforation ..	13 + 7	20%
Intestinal Haemorrhage ..	8	38%
Acute Cholecystitis	5	—

It is important, therefore, to keep a careful watch on all typhoid cases. It may be difficult to diagnose if concomitant diseases such as bacillary dysentery are present, especially during the third week, which is the common time for haemorrhage to occur. It is wise to have an initial haemoglobin estimation done on all patients, and to group their blood, as some degree of anaemia is normally present in typhoid. The anaemia is probably due in the main to a toxic effect on the bone marrow, although a mild haemolytic anaemia is also common. Care must be taken not to give blood too rapidly or in too great a quantity because of the poor state of the myocardium and lungs. There is no indication for operation as the sites of haemorrhage are usually multiple, and it would be virtually impossible to deal with them.

There were eight cases of true haemorrhage in the series with three deaths.

ACUTE CHOLECYSTITIS

This complication occurs more frequently than is generally recognized, and I have found mild right epigastric pain, associated with slight jaundice, particularly common in the acute and convalescent carrier. 13 out of 17 patients with persistent positive stool cultures were found to have more marked and more localized right epigastric tenderness than in the average case which was not excreting the bacillus. A marked degree of jaundice was seen in four such cases.

The treatment of acute typhoid cholecystitis should be conservative unless an empyema of the gall bladder makes surgical intervention imperative. The treatment of chronic cholecystitis will be discussed later, together with the problem of the carrier.

Owing to the difficulty of diagnosis of acute typhoid cholecystitis, only five undoubted cases could be included in this series.

OTHER ABDOMINAL COMPLICATIONS

On several occasions, paralytic ileus was present in very toxic patients, quite apart from those cases in which it followed a perforation.

Typhoid simulating acute appendicitis was seen on more than one occasion, but no proved case of typhoid appendicitis occurred.

It is said that peritonitis may be caused by rupture of a typhoid abscess in a mesenteric gland, but I consider that it is usually due to a small undiagnosed intestinal perforation.

GENERAL SURGICAL COMPLICATIONS OF TYPHOID FEVER

TABLE X

GENERAL SURGICAL COMPLICATIONS OF TYPHOID FEVER

	No. of Patients	*Deaths*
Typhoid Abscesses	7	—
Typhoid Arthritis	2	—
Osteomyelitis	1	—
Typhoid Spine	? 1	—
Typhoid Orchitis	2	—
Parotitis	2	1
Otitis Media	4	—
Zenker's Degeneration (Biceps)	1	—
Bed Sores	2	—
Venous Thromboses (Severe)	2	1

1. Typhoid abscess

This is a complication which is often mistaken for a boil and vice versa. The danger of it is not so much to the patient, but to those who surround

him, as a virtually pure culture of typhoid bacilli is present. Differences noted between a typhoid abscess and an ordinary boil were that the typhoid abscess was usually on a deeper plane, and usually, although not invariably, less acute. Most of the typhoid abscesses were situated in and around the buttocks, but this was not invariable, and one abscess was in the axilla and presented exactly like a boil. I would like to stress that all boils in typhoid must be regarded as typhoid abscesses until proved otherwise. On the other hand, staphylococcal boils are a fairly common complication, for in the research series 5 per cent. had moderate or severe boils.

The danger attending incision, apart from infection to the surroundings, is the poor tolerance of the patient to general anaesthesia already mentioned. The indication for incision is when the abscess is pointing; but the majority, being deep, clear up by conservative measures.

Seven cases of typhoid abscess, proved by culture, were seen among 240 cases. All seven patients were treated by repeated aspiration and systemic chloramphenicol. Five cleared up in a few days, but in two the convalescence was prolonged.

2. Arthritis

Although painful joints are a very common presenting symptom in typhoid a true arthritis is rare, and only two definite cases occurred in the series. In one patient the right sternoclavicular joint was involved, and in the other the right hip. Both these patients were treated conservatively with rest and chloramphenicol. Resolution was complete, but took many weeks to achieve.

3. Osteomyelitis

Typhoid osteomyelitis is now less common, probably because the disease is treated early with chloramphenicol. I only diagnosed one case of osteomyelitis among a total of over 1,000 cases of typhoid. This was in a convalescent patient aged 20 who presented with pain and swelling over the midshaft of his left tibia. X-ray showed an area of osteoporosis. He was treated conservatively and slowly improved over a period of weeks.

4. Typhoid spine

There have undoubtedly been true cases of typhoid spine in the past, but this is a condition which almost certainly has been misdiagnosed. It is probable that the advent of chloramphenicol has made this a very uncommon complication; but marked wasting is common in typhoid and low back strain occurs as a result. In the series 7.1 per cent. of the patients complained of backache on admission.

Only one suggestive case occurred in this series. This was in a patient aged 28, who had pain in the lower thoracic region. The X-rays were equivocal and the case is therefore unproven.

5. Typhoid orchitis

This condition is said to be rare, and only two cases were seen. Both occurred unilaterally during convalescence in patients aged 25 and 26 years respectively, who had not been treated with chloramphenicol. There was no urethral discharge. The treatment was conservative and recovery was slow, much as would be the case in a non-specific orchitis.

6. Parotitis

This occurs in any feverish illness where inadequate attention has been paid to the hygiene of the mouth, or where cachexia is common. When it occurs in typhoid it is almost certainly due to an infection by a non-specific organism, and not to the typhoid bacillus. It is a very lethal condition and often terminal, and was seen in two patients, one of whom died and the other recovered. Both were treated conservatively, but in retrospect I feel that incision under local anaesthesia should have been carried out.

OTHER SURGICAL COMPLICATIONS

Many other surgical complications of typhoid may occur, due to concomitant infection and not the typhoid bacillus, and usually associated with the poor general state and toxicity of the patient. They are, however, classical and well recognized complications of typhoid fever, and therefore will be included.

1. Otitis media

This occurred in four patients with typhoid. The pus was cultured on all occasions, and no typhoid bacilli were isolated. All were treated satisfactorily with penicillin.

2. Zenker's degeneration of muscle

No case of this was seen in the classical site of the rectus abdominis. One patient, however, was seen with marked swelling of the biceps. This was in a boy of 17 with a severe attack of typhoid. The swelling, on aspiration, yielded pure blood, and was almost certainly a tear in a partly degenerated biceps.

3. Bed sores

These are common in typhoid despite the best nursing care. In the series two severe bed sores occurred, both in patients with intestinal

perforation associated with a toxic myocarditis. This complication is mentioned merely to stress that skin grafting should be deferred until well into convalescence, because of the poor tolerance to general anaesthetics, even weeks after an acute attack of typhoid fever.

4. Venous thrombosis

Minor thromboses in the veins of the calf may be difficult to detect in a toxic patient. Major thromboses, however, may occur in large veins. Anticoagulants, though indicated in other conditions, should be used cautiously in typhoid because of the possibility of haemorrhage from the gut which may be potentially lethal. I think they should be given to the severe cases only. Major venous thromboses should be minimized by adequate hydration, general treatment including antibiotics and gentle mobilisation of the limbs. There were only two unequivocal examples of major vein thrombosis in the series. One occurred in the left femoral vein, and the patient recovered; one in the left subclavian and the patient died.

MEDICAL COMPLICATIONS

TABLE XI

MEDICAL COMPLICATIONS OF TYPHOID FEVER

	No. of Patients	*Deaths*
Typhoid Lobar Pneumonia	3	1
Typhoid Meningitis	3	1
Typhoid Nephritis	3	1
Haemolytic Anaemia ..	5	3

1. Typhoid lobar pneumonia

Seven undoubted cases occurred, and great care was taken to confirm the diagnosis. Points of interest are that the white blood count was found to be below 10,000, herpes labialis did not occur, and the patients did not respond to penicillin. Although two of these developed a pleurisy in convalescence, the complications of interest to a surgeon, namely lung abscess and empyema, were not seen.

2. Typhoid meningitis

Meningeal irritation is common in typhoid, especially in children, so care must be taken with the diagnosis. Three cases, however, of true meningitis occurred among the research series. One of the three patients died, and it is of interest that at post mortem a pure culture of salmonellae typhi was obtained from the meninges. Surgical complications such as brain abscess were not seen in the two cases that recovered.

3. Typhoid nephritis

This condition is not really of surgical interest. It must not be mistaken diagnostically for the commonly occurring small amount of albumen in the urine of toxic cases of typhoid fever. Three cases of nephritis were seen in the research series. All three patients had the typical distribution of oedema, together with albumen, blood and casts in the urine. The treatment was along the general lines of both typhoid and acute nephritis.

4. Haemolytic anaemia

A mild degree of haemolytic anaemia was not uncommon in the very toxic cases, and was presumably due to some haemolysis, in organs such as the spleen. A moderate or marked degree with jaundice was not common, however, and was seen unequivocally in only five patients, an incidence of 2 per cent. There were three deaths, thus indicating the seriousness of this complication. In only one patient was the haemolysis sufficiently large to cause haemoglobinuria. The surgical interest of this condition is that it must be considered first in the differential diagnosis of an obstructive jaundice. Pigment gall stones may also occur, although this latter complication was not seen in this series.

TYPHOID FEVER IN PRIMITIVE CONDITIONS

Typhoid fever is usually the scourge of poorly educated communities with poor hygienic habits. Hospital, laboratory, and medical personnel are often in short supply, and methods of diagnosis and treatment as advocated by most standard textbooks totally impracticable. The medical officer needs a rapid simple diagnosis, and a simple reliable treatment, supervised often by lay personnel. A number of the patients in the series were seen in primitive circumstances, and therefore the methods of diagnosis and treatment advocated are tempered by practical experience.

Diagnosis

A clinical history and examination plus a diazo test of urine will do much to clarify the position. A single specimen of blood in suitable culture media can be used for both culture and Widal reaction. Stool culture, blood for malarial parasites, and a white blood count are also useful.

Therapeutic test

As a preliminary measure in primitive circumstances only, suspected bacillary dysentery, malaria, and pneumonia may be rapidly differentiated from typhoid by their response to sulphaguanidine, mepacrine and

penicillin respectively. This should not be the routine where modern facilities are available.

Antibiotics

In primitive conditions chloramphenicol could be given in a dosage of 0.5 G. t.d.s. instead of 6–hourly.

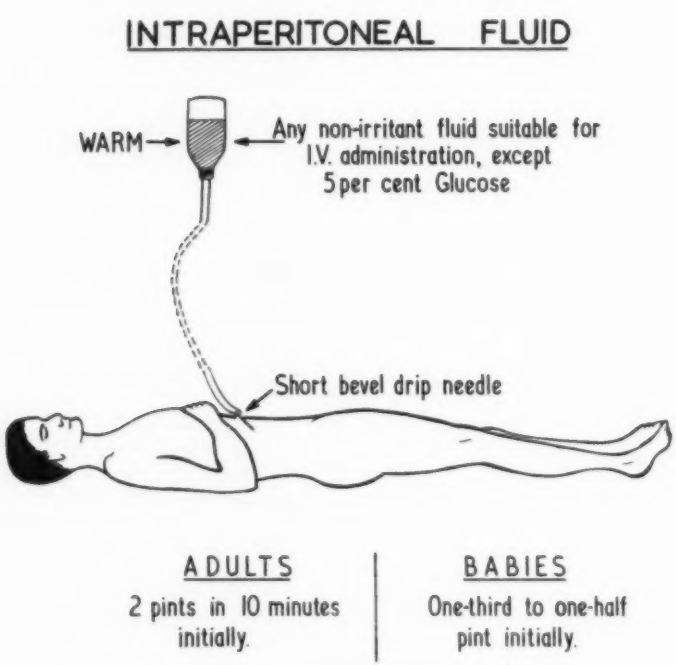

Fig. 7. Intraperitoneal fluid.

Intraperitoneal fluid (Fig. 7)

The administration of intravenous fluids, although the treatment of choice in this country in adults, is often impracticable in an epidemic in primitive surroundings. Many patients have to be treated in poorly lit mud huts by overworked surgeons and physicians, who have neither the time nor the staff to supervise an intravenous drip, and it is in these circumstances that the intraperitoneal drip comes to the fore. It is also invaluable for the treatment of dehydration in young children where adequate nursing is not available or when the veins are collapsed.

The rationale behind the use of intraperitoneal fluid is that the large peritoneal area in the abdomen will absorb as much fluid and other constituents as it requires. The effect is often dramatic although less so than by intravenous administration. I have given intraperitoneal fluid in over 200 patients, and have not experienced any complications from its use. Contraindications to this method are abdominal complications of typhoid such as intestinal perforation, peritonitis and paralytic ileus.

The great advantage of the intraperitoneal drip is the great speed at which it can be given with absolute safety, and with no danger of overloading the circulation (2 pints of fluid in 10 minutes in an adult). It also requires little technical skill, and a nurse can easily master the method. Boiled tap water can even be given in an emergency if nothing better is available. There is no worry about confused patients pulling out a drip needle or of veins thrombosing.

The method of administration is by an ordinary short bevel drip needle inserted obliquely in the midline of the upper abdomen. It should be nearer the xiphisternum than the umbilicus to minimize the risk of injuring the bowel although this must be rare. No anaesthetic is required for the ordinary toxic case or baby, although a little 2 per cent. Xylocaine is kinder for other patients. The needle should be inserted with fluid running slowly out of it. Once inserted, if the fluid does not run continuously on turning up the drip, the usual cause is that the needle is still in the abdominal wall. The fluid should preferably be warmed to the temperature of the body before administration and run in with the clamp fully open. Depending on the head of pressure and size of needle the administration of 2 pints requires about 10 minutes. The needle is then pulled out and the procedure is repeated as required.

The amount of fluid is gauged by the amount of dehydration, and the size of the patient. One-third to one-half pint for a small baby, 2-3 pints for an adult, given fast, is a safe initial amount. 0.45 per cent. saline is the best fluid for routine administration, but normal saline, 2.5 Glucose, Hartmann's solution and plain sterile water can all be used; even ordinary tap water was used on one case in an emergency, with no harmful effects. 5 per cent. Glucose in water (isotonic) should not be used for prolonged administration because electrolyte loss may occur into this from a plasma already deficient in these essential constituents. For repeated administration as in the case of intravenous fluid, care must be taken to assess the relative fluid and electrolyte state of the patient.

With due regard to its occasional limitations, intraperitoneal fluid should prove of considerable value, especially in adults in more primitive conditions, and in children everywhere, and with the exceptions mentioned, irrespective of the disease responsible for the dehydration.

TYPHOID IN CHILDREN

The clinical diagnosis differs from the adult in that the onset is much more acute, and an enlarged tender spleen very commonly found. 56 children under the age of 16 were seen with typhoid, but only six of these were under five. The diazo reaction of urine proved of great value and, from a practical aspect, the stool culture better than the blood culture. Dehydration often necessitated urgent treatment, and the intraperitoneal drip proved of inestimable value. A liquid preparation of chloramphenicol, " chloromycetin palmitate ", was found well tolerated, even by small children. The complication rate was found to be no higher than in adults, but in view of the speed of progress, treatment, to be effective, had to be adequate and early.

THE CARRIER

Urinary carrier

The chronic urinary carrier can usually be cleared by chloramphenicol (Miller and Floyd, 1954, Lewin *et al.*, 1951, McLintock, 1950), and is not much of a problem. The occasional refractory case with renal damage may require a pyelolithotomy or nephrectomy (El Sadr, 1953).

Faecal carrier

The faecal carrier is a much more difficult problem, and has in the past often been thought to necessitate a cholecystectomy. This has been far from the complete answer, however, and in a definite percentage it fails completely. Chloramphenicol on its own has very little effect (Manson-Bahr, 1958), and even cholecystectomy with chloramphenicol cover may sometimes fail (Carnes *et al.*, 1954/1955). The problem was, therefore, investigated with two series of cases (Table XII).

TABLE XII

CONSERVATIVE TREATMENT OF THE FAECAL CARRIER

Aureomycin and Chloramphenicol

		No. of Patients	*No. Cured*
Series I	Acute Disease	11	8
Series II	Convalescent Carriers	9	6

Series I consisted of a trial to prevent the carrier state from occurring in the first place. 11 patients with acute typhoid fever, all of whom were excreting the bacillus, were treated with a combination of 0.5 G. each of aureomycin and chloramphenicol for 7 days. Eight out of 11 of these ceased to excrete the bacillus.

Series II consisted in treating nine persistent convalescent carriers with combined aureomycin and chloramphenicol, and six out of nine were cleared.

It was felt that a longer course than seven days might have cleared both series completely.

It is concluded that in a chronic carrier, a course of combined aureomycin and chloramphenicol should be tried for 2-3 weeks before surgery is contemplated. If this fails, cholecystectomy should be carried out, the operation being covered by a combination of aureomycin and chloramphenicol. In the case of stones or other definite pathology in the gall bladder, early cholecystectomy should be done, again covered by the above two chemotherapeutic agents.

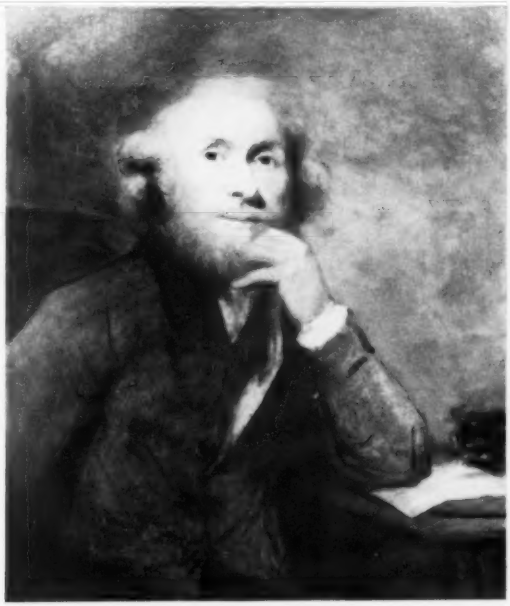

Fig. 8. John Hunter—in his later years—by Reynolds.

CONCLUSION

It may be thought that one has spared the knife too much from these patients, and tended to advocate conservative treatment where operation hitherto has been the more accepted treatment. Acceptance of a method, however, does not necessarily mean that it is either good or immutable,

and the results of operations based on analogy with other abdominal emergencies have been anything but encouraging.

Typhoid fever differs in many aspects from the diseases and surgical conditions which it may mimic, as John Hunter recognized (Fig. 8). The friable lower ileum, multiple-perforated and chloramphenicol sterilized, is a completely different entity from the peptic perforation of stomach or duodenum.

The simpler methods of treatment such as intraperitoneal fluid have been stressed for those of us who have worked, or will work, in countries where typhoid is endemic and occasionally epidemic. The necessity is for speed and simplicity, with safety.

The most important thing that I have gained from my experience in this investigation has been an appreciation of the value of conservatism in the management of the surgical complications of typhoid fever. Otherwise our patients might echo those famous words of Mark Antony:

"*This was the most unkindest cut of all*".

ACKNOWLEDGMENTS

I should like to take this opportunity of thanking Mr. D. B. Cater, F.R.C.S., and Dr. F. J. Wright, F.R.C.P., for their help, advice and encouragement, Dr. E. R. N. Cooke for the pathological investigations, and the Director of Medical Services, Kenya, for granting me the facilities for this research. I should also like to thank the Surgeons and Physicians of the King George VI Hospital, Kenya, and many friends both in this country and in East Africa for their help.

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VAGAL NERVE SECTION
IN CHRONIC DUODENAL ULCERATION

Hunterian Lecture delivered at the Royal College of Surgeons of England

on

5th November 1959

by

H. W. Burge, M.B.E., F.R.C.S.

Surgeon, West London Hospital

FOR TWELVE YEARS at the West London Hospital we have studied the operation of vagotomy in duodenal ulceration, and I wish in this lecture to put before you the results of these studies and to tell you the conclusions we have drawn from them.

I will not dwell on the history of vagal nerve section before Dragstedt, although it was used by surgeons as early as 1912. If the operation is of value we must thank Lester Dragstedt, for it was his unusual combination of physiologist and surgeon which was to write what might prove to be one of the greatest chapters in the history of gastric surgery.

In 1947 I came to use the operation in cases of chronic duodenal ulceration, and used it then, as did others, without gastric drainage. By the time we were aware of the unpleasant side effects of this form of operation, and had learnt to add gastric drainage in all cases, the operation was already falling into disrepute. During the years that followed, the memory of the unpleasant effects of the undrained stomach, and a few reports of the risk of recurrent ulceration, killed the operation for all but a few. Throughout the surgical world it was discarded, but discarded without proper study. Only a few voices still cried out in the surgical wilderness.

On this but slender evidence, I reverted in 1950 to the operation of subtotal gastrectomy, using vagal nerve section for cases of anastomotic ulceration after gastric resection. The wonderful results of vagal section in this condition seemed to indicate that we had here, in fact, a very powerful weapon. In that same year we planned a nation-wide study of the results of vagotomy. With the cooperation of surgeons in many cities, Mr. Alan Pollock, F.R.C.S., gathered together some 1,500 cases of all types. These he studied, and he published his findings (Pollock, 1952). We filed away these records and continued for five years to use subtotal resection. After that time, Mr. John Lloyd Davies, F.R.C.S., studied again Pollock's series (Lloyd Davies, 1956). He studied only those cases in which gastric drainage had been established, either by gastrojejunostomy or by pyloroplasty. His five-year results seemed so

good that I once more abandoned gastrectomy. Tables I and II summarize his findings. It will be seen that few cases were untraced in this five-year review, and the proved recurrence rate, both after gastro-jejunostomy and after pyloroplasty, was low.

TABLE I

VAGOTOMY AND GASTRO-ENTEROSTOMY

(Five years)

Total number	212	
Lost to follow-up	6	2.8%
Dead (other causes)	13	6.2%
Proved recurrence (anastomotic ulcer)	7	3.5%
Gastric ulceration	2	1.2%
Stenosis requiring surgery	0	0.0%

TABLE II

VAGOTOMY AND PYLOROPLASTY

(Five years)

Total number of cases	140	
Lost to follow-up	8	5.7%
Dead (other causes)	7	5.0%
Proved recurrent D.U.	4	3.2%
Gastric ulceration	2	1.6%
Stenosis requiring surgery	1	0.8%

Two years later Dr. Ernest Pick and I studied again the series with gastro-enterostomy (Burge and Pick, 1958). We were fortunate in obtaining permission to include a further series of Pollock's original cases which were not included in the five-year review. No case was now less than seven years after operation, and most were eight or nine. Table III shows the results of this study.

TABLE III

VAGOTOMY AND GASTRO-ENTEROSTOMY FOR DUODENAL ULCER

Total number in series	301
Shortest follow-up	7 years
Number untraced	6
Died from other causes	13
Followed 7 to 9 years	282
Proved recurrence rate	4.5%

Recently Dr. Peter Clark and I have completed the ten-year review of both series, and the results are shown in Tables IV and V (Burge and Clark, 1959). No proved recurrence has occurred since the five-year study and it will be seen how low the proved recurrence rate is at ten years and how few cases are untraced.

TABLE IV

VAGOTOMY AND GASTRO-ENTEROSTOMY

(Ten years)

Total number	301	
Lost to follow-up	11	
Dead (not from ulcer)	28	
Number followed	262	
Recurrent ulcer (anastomotic) ..	10	3.8%
Gastric ulcer	2	.7%
Later operation for stenosis ..	1	.3%

TABLE V

VAGOTOMY AND PYLOROPLASTY

(Ten years)

Total number	140	
Lost to follow-up	7	
Dead (not from ulcer)	7	
Number followed	126	
Recurrent ulcer (excluding gastric ulcer) ..	4	3.1%
Gastric ulcer	3	2.3%
Later operation for stenosis ..	6	4.7%

It was impossible to determine accurately the incidence of incomplete nerve section in the series, but from insulin test meal studies, and from our own observations, we estimated that at least 30 per cent. of these cases were left with one or more undivided nerve trunks.

We have compared carefully the results of gastric resection and vagotomy. I will not discuss this comparison in detail in this lecture, except to say that in respect of mortality, of dumping, of weight loss, and of late anaemia, vagotomy with gastric drainage proved the better operation. Only one feature seemed to weigh against vagal nerve section. This was the incidence of disturbance of bowel function. Both at five years and at eight years, some 30 per cent. of patients stated that they had some diarrhoea or loose motions. When this 30 per cent. was studied in detail, several important facts emerged. Many patients were pleased that their pre-operative constipation was cured. Some, however, had mild attacks of diarrhoea lasting one to three days and occurring often at two- or three-monthly intervals. The stools were pale and bulky. The incidence of severe diarrhoea has been very low—probably not more than 2 to 3 per cent. Some patients found early morning diarrhoea troublesome, but after one or two motions they were free from trouble for the rest of the day. Diarrhoea is an interesting complication, because, as with dumping after gastrectomy, a surgeon may remain quite unaware of its presence in his cases. However, careful study and questioning will, without fail, bring it to light. Many papers have been written on this subject. Ruffin and Smith (1946) reported it in 40 per cent. of cases. Smith *et al.* (1947) in 50 per cent. and Collins *et al.* (1948) in 36 per cent. These figures agree very closely with our own.

We studied this symptom in two hundred cases of gastrectomy, and found exactly the same incidence of change in bowel habit and exactly the same syndrome, but the picture seemed a less severe one after gastrectomy than after vagotomy. Barium studies did not suggest gastric delay as a cause of post-vagotomy diarrhoea.

Two problems, it seemed, needed solution. The first was to overcome the high incidence of incomplete nerve section, and the second to find the cause of, and so perhaps to prevent, post-vagotomy diarrhoea.

The problem of incomplete nerve section

Many papers have been written condemning the operation of vagotomy on its recurrence rate, without discussing the problem of incomplete nerve section. Dragstedt *et al.* (1951) stated that persistent or recurrent ulceration was almost invariably due to incomplete vagal nerve sections.

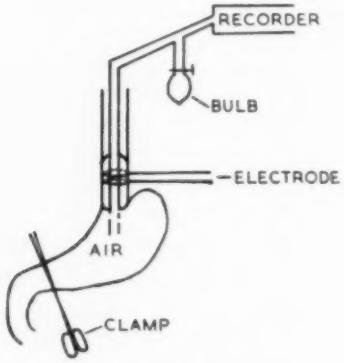

Fig. 1.

Stempien and Weinberg (1953), in their paper on recurrence of ulcer after vagotomy, described eleven cases where further operation had been undertaken. The right vagus was found intact in six of these cases, and the left vagus intact in one. In one case a small intact nerve was found. In two cases, adhesions prevented a search for the nerves, and in one case no intact vagus was identified. Stempien *et al.* (1959), giving the five-year results of vagotomy and pyloroplasty, found a proved recurrence rate of 4.8 per cent. with an incomplete nerve section rate, as shown by the insulin test meal, of 38 per cent.

The Hollander insulin test meal for completeness of nerve section can be used only after operation and is in some ways unsatisfactory, for false negative findings can arise because of the gastric drainage procedure.

Dr. John Vane and I, working initially on cats, evolved a test which can be used to demonstrate complete nerve section during operation. Figure 1 shows the principle of this test. I will not describe it here in detail, for it has already been published (Burge and Vane, 1958). An electrode divided into four quadrants is placed around the lower oeso-

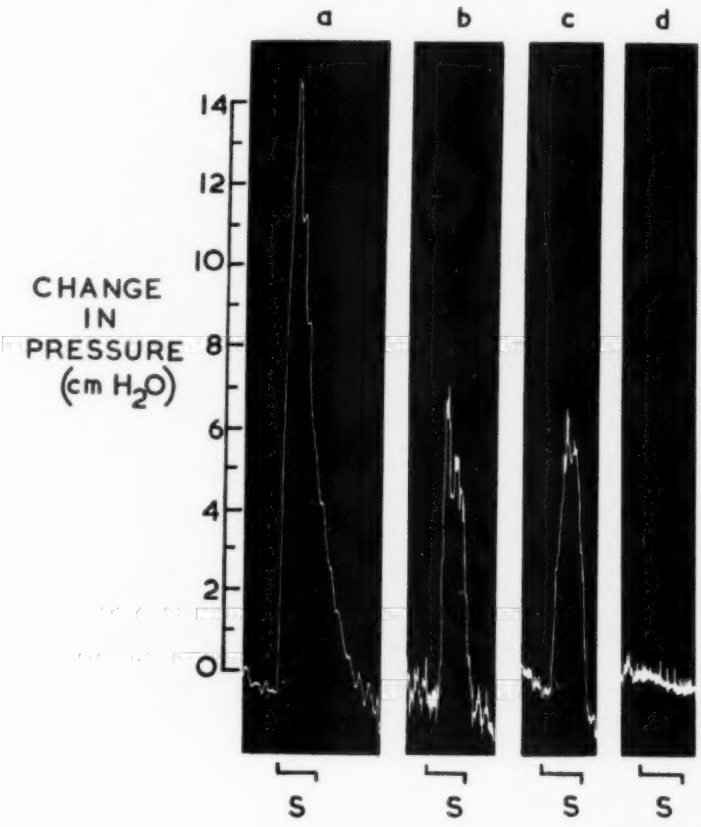

Fig. 2.

phagus. This is best done after the anterior vagus has been divided. The intra-abdominal oesophagus is then longer and the electrode is more readily applied. The surgeon can easily be sure that all posterior nerves lie within the electrode. A cuffed gastric tube is placed in position, and the cuff inflated to seal the lower oesophagus and to bring the vagus nerve

trunks into contact with the electrode. A clamp is placed across the gastric antrum and, with the gastric tube connected to a water manometer, the stomach is distended with air. On stimulation of the electrode, undivided nerve trunks will be demonstrated and can be localised to their quadrants by an increased pressure in the water manometer. Figure 2

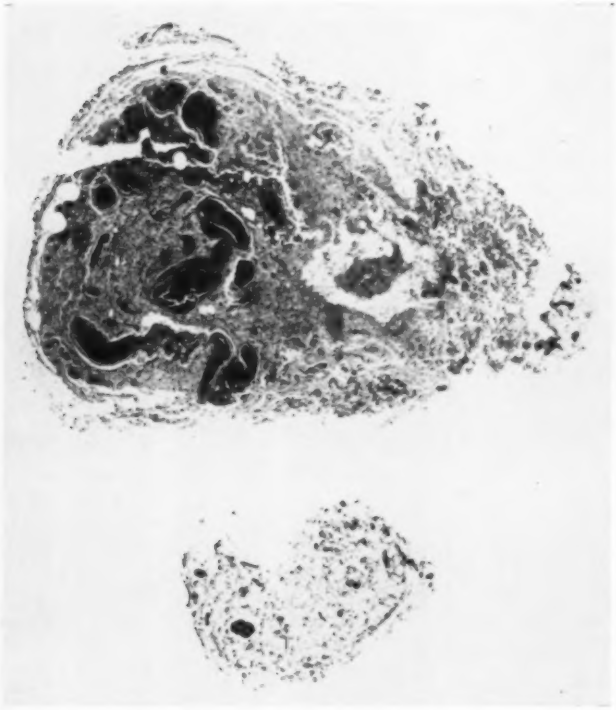

Fig. 3.

shows a recording in man. After division of three trunks complete nerve section was obtained. This test has proved extremely sensitive. In Figure 3 the larger nerve is an average main vagal trunk. The lower one consists of two small nerve bundles. It was demonstrated and localized and gave rise to an increase of 1 cm. of water pressure. Figure 4 shows the apparatus as now used. It contains a transistorized stimulator and a water manometer in which respiratory movement during recording is damped out.

I am often asked if I think this test is necessary. Jackson (1948), in describing the anatomy of the vagus nerves, showed how frequently both the anterior and posterior nerves were present as multiple trunks. The frequency of multiple trunks, together with repeated references in the literature to a high incidence of incomplete nerve section, answers clearly this question. I have already quoted the operative findings of Stempien and Weinberg in their series of recurrent ulceration. It is true that a surgeon very experienced in vagotomy rarely needs it, though even he may miss small nerve trunks. Surgeons less experienced in the operation most certainly need a test during operation.

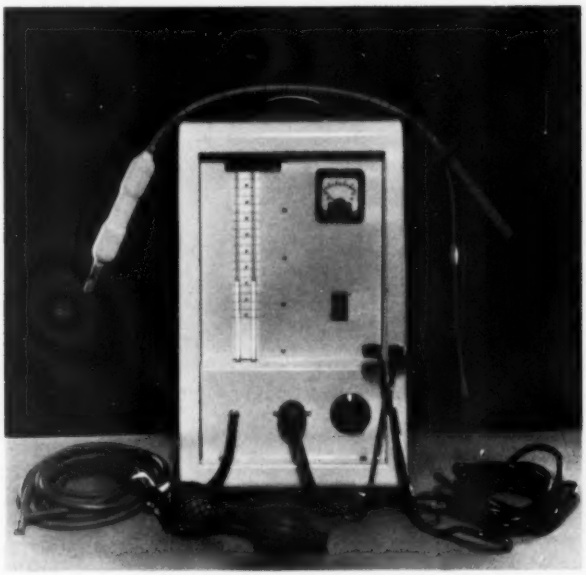

Fig. 4.

We know gastrectomy need not be total to cure almost all duodenal ulcers and in the same way probably vagotomy need not be quite complete. The low recurrence rate with a high incidence of incomplete nerve section in our ten-year results suggest that this is so. Nevertheless, there is evidence that in the same way as a small trunk can produce a considerable motor response, so too a small trunk can produce a considerable secretory response. It is important, therefore, that we should aim at complete gastric vagotomy, and it would seem only reasonable to use a test during operation to make sure that this has been achieved.

The problem of post-vagotomy diarrhoea

Because of the great excess of faecal fat in cases after vagal nerve section, we suspected that pancreatic deficiency following vagotomy was the cause of this symptom, and that perhaps it could be prevented, or at least modified, by selective vagotomy. Figure 5 shows the main features of the anterior vagus nerve. It will be seen that it gives off a hepatic branch which runs to the liver in company with a small artery which is a

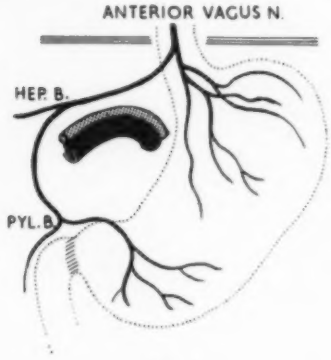

Fig. 5

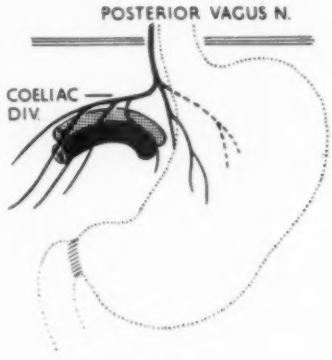

Fig. 6.

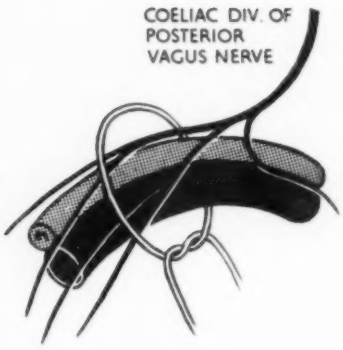

Fig. 7.

branch of the ascending branch of the left gastric vessel. This hepatic branch gives off a pyloric branch, which descends to the upper border of the pylorus and which gives branches ascending the lesser gastric curve. These seem constant branches and can be seen at operation. The gastric branches of the anterior nerve are usually multiple. Figure 6 shows the distribution of the posterior nerve. A large part of this nerve runs on as

the coeliac division to the coeliac plexus. The gastric branches are multiple, and indeed gastric branches often arise from the coeliac division. It is interesting to note that when the left gastric artery is tied flush with the abdominal wall during gastrectomy, the ligature includes the coeliac division of the vagus (Fig. 7).

In an attempt to overcome the side-effects of the operation, selective vagotomy was used by Jackson as early as 1948 (Jackson, 1948). It was used also in six patients in the same year by Franksson (1948). Neither of these workers, however, seemed to have associated such an operation specifically with the prevention of post-vagotomy diarrhoea. In using it ourselves, we first divided the anterior nerve completely and preserved

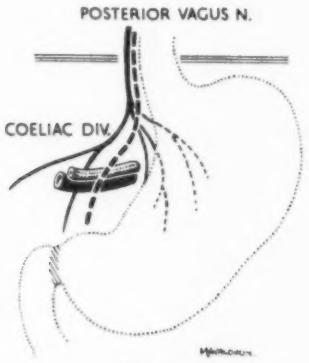

Fig. 8.

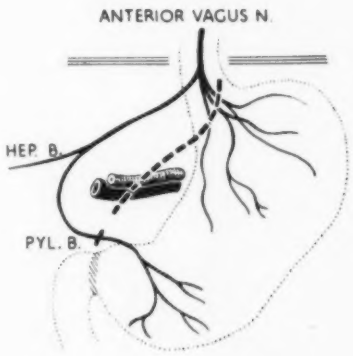

Fig. 9.

the coeliac division of the posterior nerve. In doing this it is important to divide the left gastric artery and vein (Fig. 8). It is not possible, because of variations in the anatomy of the nerve, to divide the gastric branches completely and to retain the vessels. At one time we thought that this operation might completely prevent post-vagotomy diarrhoea, but later we found that this was not so.

We next applied selective vagotomy to the anterior nerve as well as to the posterior, and retained the hepatic branch while dividing all the gastric branches (Fig. 9). We have dealt with the pyloric branch by dividing its gastric branches at the pylorus, but it may well be that it is better dealt with by dividing the pyloric branch itself. This is easily done, for when preparing the duodenal stump in gastrectomy, this nerve is necessarily divided.

Figure 10 shows the incidence of even the most mild symptoms of diarrhoea in the three operations.

(a) In complete vagotomy of all nerves, as shown by test.
(b) Complete gastric vagotomy with preservation of the coeliac branch of the posterior nerve.
(c) Selective vagotomy applied to the anterior and posterior nerves, with division of gastric branches and the pyloric branch.

In all these cases, gastric drainage has been obtained by posterior gastro-enterostomy.

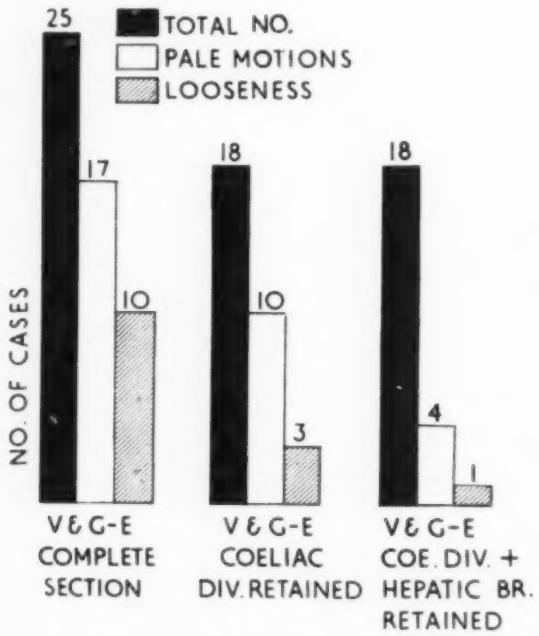

Fig. 10.

We have not yet investigated the incidence of this symptom when gastro-enterostomy is done without vagotomy. Our series of selective vagotomy is not yet big enough to allow of a definite conclusion, but there is evidence that selective vagotomy may play an important part in the prevention of diarrhoea. We hope before long to establish this point beyond doubt.

My remarks in connection with post-vagotomy diarrhoea have so far referred to a change of bowel habit brought about by division of the

vagus nerves. I cannot, however, leave this subject without mentioning the problem of infective diarrhoea arising in the early post-operative days. We have two cases in which an infection with Salmonella Typhi Murium occurred, and in one of these the condition proved a very serious one. It would seem that the reduction of acid following vagotomy may allow such infections to gain a foothold. Other workers, too, seem to have had this experience, and I mention it in this lecture so that others may bear in mind the possibility of such infections following vagotomy. The stools in this condition are offensive, and with care the organism should be isolated from them without difficulty.

Gastric drainage

This lecture would not be complete without some consideration of the relative merits of the different kinds and different techniques of gastric drainage. The next two Tables, VI and VII, show again the ten-year results.

TABLE VI

VAGOTOMY AND GASTRO-ENTEROSTOMY

(Ten years)

Total number	301	
Lost to follow-up	11	
Dead (not from ulcer)	28	
Number followed	262	
Recurrent ulcer (anastomotic) ..	10	3.8%
Gastric ulcer	2	.7%
Later operation for stenosis ..	1	.3%

TABLE VII

VAGOTOMY AND PYLOROPLASTY

(Ten years)

Total number	140	
Lost to follow-up	7	
Dead (not from ulcer)	7	
Number followed	126	
Recurrent ulcer (excluding gastric ulcer)	4	3.1%
Gastric ulcer	3	2.3%
Later operation for stenosis ..	6	4.7%

It will be seen that the incidence of gastric ulceration was virtually none in the gastro-enterostomy series, but was 2.3 per cent. when pyloroplasty was used. In all these cases of gastric ulceration there was pyloro-duodenal stenosis. In pyloroplasty it seems that this was brought about either by performing the operation in the presence of duodenal stenosis or by the faulty performance of the pyloroplasty. It is interesting to note that, in each case in this series, secondary gastrectomy was not done until five or more years later. Stenosis following gastro-enterostomy can only

occur when two small a stoma is made in the presence of duodenal obstruction; this is liable to happen if an attempt is made to place the stoma very close to the pylorus posteriorly.

In the pyloroplasty series there was a small incidence of death from leakage. This was absent from the gastro-enterostomy series.

Both pyloroplasty and pylorectomy seem satisfactory operations, if well done, as forms of gastric drainage, but considerable experience is needed if these operations are to be performed with no risk of leakage or of late stenosis.

I will not discuss all the problems of gastro-enterostomy, though these are many. However, if it is used, an adequate stoma is necessary, especially if duodenal stenosis is present. It must certainly not be placed too high, and it is probably best placed as close to the pylorus as is compatible with an opening of sufficient size. The operation had a chequered history from 1880, when it was first performed, until the nineteen-twenties, when Moynihan laid down the principle of the posterior vertical stoma. We, too, have seen many of the complications encountered during these years. We have seen the efferent loop adhesive block in the anterior oblique anastomosis, and the afferent limb block from too tight a loop. We have seen trouble from a loop twisted inadvertently at the time of operation. Trial and error have led us to support the vertical posterior anastomosis of good size, with a not too short afferent limb. The so-called vicious-circle vomiting of the past would seem to be nothing more than an obstructive phenomenon of the afferent or efferent limb.

We have not used pyloroplasty as a method of gastric drainage, but have used pylorectomy in a number of cases. Excision of the pyloric muscular ring anteriorly seems a better operation than pyloroplasty.

Gastric aspiration

After operation we have used gastric aspiration, giving fluids by mouth from the first post-operative day. The Ryles tube is withdrawn when the " gastric balance " is well positive. Almost invariably the tube is withdrawn 36 hours after operation. In cases where it has been necessary to retain the tube for a longer period, there has usually been some kind of complication. I do not think that a gastrostomy at the time of operation, no matter how small, is a desirable method of gastric decompression, when a Ryles tube can be used and withdrawn in so short a time.

Vagotomy and gastric drainage in perforated duodenal ulcer

When perforation of a duodenal ulcer takes place in a patient who has already a long history, with great disability, or who already has duodenal stenosis, many surgeons would perform an immediate partial gastrectomy.

This has proved a very satisfactory method of treatment. In such cases we have sutured the perforation and performed immediate selective vagotomy and gastro-enterostomy, proving completeness of nerve section by the stimulation test. It would seem that the only factor which could weigh against such a procedure would be the exposure of the retroperitoneal areas in a patient liable to sepsis. This is a method which cannot however be assessed at present, but no doubt further experience may well indicate that it is a very satisfactory method of treating such cases.

I have now put before you the results of our studies so far as they have gone. There are still problems which we hope to solve in due course. From our studies we have drawn the following conclusions:—

(1) That complete vagal nerve section is the treatment of choice when surgery is indicated in chronic duodenal ulceration. We have not considered it reasonable to use it in cases of massive haemorrhage requiring urgent surgery, nor have we used it when gastric ulceration is also present.

(2) That without a test for complete nerve section which can be used during operation there is risk of incomplete nerve section, perhaps leading to recurrent ulceration.

(3) That post-operative diarrhoea is the only sympton which weighs against vagotomy as compared with gastrectomy.

(4) That there is evidence from our studies that selective vagotomy with complete gastric vagal section may be important in the control of post-vagotomy diarrhoea. The present evidence, based on our small series of cases, suggests that both the coeliac division of the posterior nerve and the hepatic division of the anterior nerve should be preserved.

(5) That there is no need to combine vagal nerve section with excision of the gastric antrum, or to perform a low gastrectomy. Complete vagal nerve section needs no more than a good gastric drainage procedure. The operation of low gastrectomy and vagotomy has probably arisen because of rather high recurrence rates recorded in some series of vagotomy with gastric drainage. It seems that this recurrence rate has been due to incomplete section.

The operation of sub-total gastrectomy for chronic duodenal ulceration has been a planet in our universe. It was evolved as a great experiment, by trial and error, in the laboratory of human life. Vagotomy, in spite of its sound physiological basis, must in the end be assessed in the same way. Indeed, the experiment is already drawing to a close. Gastric resection is passing into the shadows of the past. Let us hope that incomplete nerve section will not dim the brilliance of our newest star.

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FACULTY OF ANAESTHETISTS

AT A MEETING of the Board of Faculty of Anaesthetists on 16th March, Dr. G. S. W. Organe was re-elected Dean for the year 1960–1961, and Dr. H. J. V. Morton was elected Vice-Dean in place of Professor E. A. Pask, who has retired from the Board of Faculty in rotation.

On 9th March, the postal ballot for election to the Board of Faculty was held, and the following candidates were successful:

Dr. J. A. Lee
Dr. W. D. Wylie
Dr. M. D. Nosworthy (re-elected)
Dr. G. Jackson Rees
} representing the Fellows in the Faculty

Dr. R. V. Sturton, representing the Members of the Faculty.

The thirteenth Anniversary Dinner of the Faculty was held on the evening of 16th March and there were 266 present. The toast of "The Faculty" was proposed by Sir Ivan Magill, K.C.V.O., F.R.C.S., Hon. F.F.A.R.C.S., and the Dean replied. The toast of "The Guests" was proposed by Dr. A. J. W. Beard, and Dr. C. P. Harris, Vice-Chancellor of the University of London, replied on their behalf.

THE CELLULAR ANATOMY OF EXPERIMENTAL WOUND HEALING

Arris and Gale Lecture delivered at the Royal College of Surgeons of England

on

17th December 1959

by

R. M. H. McMinn, M.D., Ph.D.

Lecturer in Anatomy, University of Sheffield

I WOULD LIKE to express my gratitude to the Council of the College for the honour they have done me in allowing me to take part in this series of Lectures. It will no doubt surprise many of what I may call with great respect the older generation that an anatomist should be interested in wound healing and tissue repair, but I think that many of them would be surprised to learn what can go on in Anatomy Departments nowadays. However, this is but a reflection of the present trend of integrating individual disciplines in our attempts to advance biological knowledge, and as an anatomist I therefore make no apology for entering a field that might more properly be said to belong to the experimental pathologist or experimental surgeon. All who are interested in biological problems must eventually meet at the cellular level or even at a sub-cellular molecule of nucleic acid, and wherever an anastomosis of anatomists is gathered at the present time the talk is as likely to be of the chemical or molecular elements of bodily make-up as it is of the grosser units more traditionally associated with the anatomist.

It is essentially of cells and their behaviour that I wish to speak this evening, and while the members of the mammalian Order cannot compete with their more humble brethren such as amphibians in their capacity to regenerate major portions of the body, more limited reparative processes are essential for the survival of the animal. At the time of the foundation of this series of Lectures in the Barber-Surgeons Company in the middle of the 17th century, the barber-surgeons must have been at least cognizant of the gross aspects of wound healing even though the cytological features were denied them. It was not until 1827 that the first purely histological paper on animal tissues was published, and this was a joint paper by Dr. Thomas Hodgkin, of disease fame, and Joseph Jackson Lister, the father of the famous son, whose interest lay in the development of the microscope and its lens systems. It was only some years later that microscopes came into more general use for purposes of teaching and illustration. From the recent fascinating book by Hughes (1959) on the history of cytology, I should like to abstract with due acknowledgment a quotation from Tuckwell's Reminiscences of Oxford concerning the early use of micro-

scopes for purposes of illustration: the lectures " were delivered in the downstairs theatre, whence we ascended to the room above, to sit at tables furnished with little railroads on which ran microscopes charged with illustrations of the lecture, alternatively with trays of coffee ". This evening I have lantern slides instead of microscopes, and perhaps by the time this lecture is over we shall all need something more than coffee.

The ready accessibility of skin for experiment and observation no doubt accounts for the fact that the majority of studies on wound healing have been carried out on this tissue. In the report of the Ciba Foundation Clinical Forum on wound healing it was stated: " To what extent findings based upon the study of lesions in skin are applicable to other tissues of the body is a question which cannot, as yet, be answered with certainty " (*British Medical Journal*, 1956).

For some years now my colleagues and I have been studying the cytology of repair in the mucous membranes of abdominal hollow viscera, in an attempt to get beyond skin. Although it is very well established through surgical practice that epithelia and connective tissues exhibit sufficient reparative powers for surgical purposes, the cellular details of such repair have not often been studied in these organs. Of all the viscera the stomach has probably received the greatest amount of experimental attention in view of the problems of peptic ulceration in man, but even here most workers have been more concerned with mechanisms of ulcer production rather than with repair processes.

I will mention first some of the cellular aspects of wound healing as they are found to occur in skin, and then proceed with our observations on abdominal viscera. I would like in the time available to deal with just a few features of repair in a number of organs rather than to concentrate on too many details in any one tissue. All the experimental lesions I shall mention are those involving loss of substance with healing by granulation. Most, but not all, of the experimental work has been carried out on the cat, whose size, without being unduly large, enabled us to make lesions of equal size in all the organs in which we were interested. This series of studies was begun in Sheffield on the small intestine with Dr. J. E. Mitchell, now a Fellow of this College, and all the remainder have been and are being carried out in collaboration with my former colleague, Dr. F. R. Johnson, now Reader in Histology at the London Hospital Medical College, and I am particularly grateful to him for allowing me such free use of our joint material for this lecture.

Skin

The epidermal cells at the edge of a wound undergo both hypertrophy and hyperplasia, resulting in a considerable thickening of the marginal skin. It is from this thickened epidermis and from hair follicles in the

vicinity that cells migrate over the floor of the lesion. Mitotic activity is most often seen in the basal layer, but proliferation can also occur at more superficial levels. While the migration is said to consist of a single layer of flattened cells in the first instance, this does not always appear to be so, especially where the cells may be obstructed by fibrin clot. There is some evidence that migrating cells may secrete a fibrinolytic enzyme although its nature is purely speculative. It should be noted that these migrating cells appear to be devoid of mitotic activity until several days after they have become fixed to the underlying tissue (Ivy *et al.*, 1952), and the absence of mitosis at this stage has been held to be one of the characteristic features of wound healing.

A further characteristic of epidermis during repair is the accumulation of glycogen. This substance is barely detectable histochemically in the

Fig. 1. Hypertrophic epidermal cells at the margin of a skin wound, showing glycogen accumulation. PAS. (×740.)

normal skin of man or other mammals, but where there is hypertrophy, whether at the site of injury (Bradfield, 1951) or in skin diseases associated with proliferation (Fanger and Barker, 1957), it can be found in considerable quantities (Fig. 1). The glycogen persists in the new epidermis as long as keratin formation is absent, but when keratin begins to be reformed the glycogen disappears. Thus there is a considerable alteration in carbohydrate metabolism in hypertrophic epidermal cells. As far as protein metabolism is concerned, a number of workers have been able to demonstrate an increase in ribonucleoprotein (RNA), which is what one might expect if cells are enlarging or dividing (Brachet, 1957).

While these epithelial changes are going on, in the subepidermal and subcutaneous tissues during the repair of a wound with loss of substance

there occurs a series of changes resulting in the formation and maturation of granulation tissue. There is proliferation of connective tissue elements with the formation of new fibrous tissue cells, blood vessels, reticulum and collagen fibres, all embedded in a matrix or ground substance that contains neutral and acid mucopolysaccharides as indicated by material that is PAS-positive and metachromatic. All this activity begins very early, and it seems entirely inappropriate to continue to use the term "lag phase" that is so often applied to the early stages of repair. I will speak later about the possible origin of the new connective tissue cells. Of the many other items that could be mentioned with regard to new connective tissue, I wish at present to refer to only one, namely alkaline phosphatase. Clinicians are familiar with this enzyme from the changes in serum levels in various diseases, and it has a well established role in bone formation. The part it may play in the formation of fibrous tissue is not yet entirely clear, for in skin wounds in the cat the enzyme cannot be detected histochemically in maturing granulation tissue, whereas in similar circumstances in rodents it is abundant (Johnson and McMinn, 1958).

Thus to summarize some of the cytological features of repair in skin and connective tissue, we may note hypertrophy and hyperplasia of marginal epidermal cells; an absence of mitosis in migrating epidermal cells; a striking glycogen accumulation in hypertrophic epidermis; and the maturation of granulation tissue with possible species differences with regard to alkaline phosphatase.

Urinary bladder

By way of leading on to the first abdominal viscus with which I wish to deal, namely the urinary bladder, I would like to remind you that epithelia are known to possess a certain specificity of behaviour, in that their cells behave in a similar manner whether they are in their normal site or in an abnormal one. For example, when a fragment of skin is implanted into the anterior abdominal wall, epidermal cells grow out from the margins of the implant to form a cyst. During cyst formation, the cells show some of the characteristic features that have been mentioned above, such as hypertrophy, migration without mitosis and glycogen accumulation. In the course of investigations on implants of bladder mucosa (Johnson and McMinn, 1955), we noted many mitotic figures in the migrating epithelial cells that were moving from the edges of the implant in the process of cyst formation (Fig. 2). It was this finding in implanted bladder mucosa that led us to investigate the healing of artificial lesions in the bladder itself (McMinn and Johnson, 1955).

Within 24 hours of removing a small area of mucosa from the bladder, epithelial cells begin to move over the floor of the lesion. There is very little mitotic activity in normal transitional epithelium, but at the margin

of the wound there is a considerable increase, and individual cells become enlarged. Furthermore, many mitotic figures can be noted in migrating epithelium at 48 hours and later—a distinct contrast to the behaviour of epidermis. The fully epithelialized wound site at the end of one month shows rather characteristic, crypt-like downgrowths of epithelium, such as Johnson (1957) has described in correlation with cystitis glandularis and related conditions.

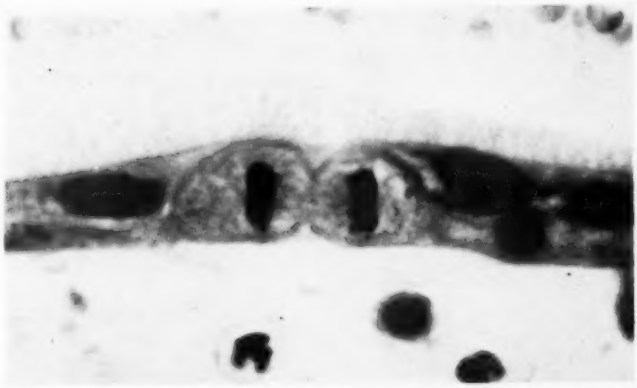

Fig. 2. A cell in the telophase stage of mitosis, in a sheet of epithelial cells migrating from the margin of an implant of bladder mucosa. H. and E. (×1700.)

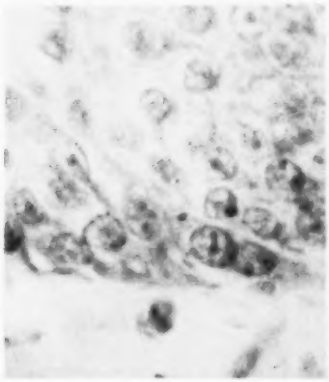

Fig. 3. Hypertrophic epithelial cells at the margin of a wound in the urinary bladder. Compare with Figure 1, and note the absence of glycogen. PAS. (×740.)

With regard to histochemical changes, normal bladder epithelium contains PAS-positive material, most but not all of which is glycogen, and from the known facts about epidermis we expected to find an increase in the glycogen content during repair. To our surprise exactly the opposite is the case (Fig. 3). The histochemical tests for glycogen have been repeated many times with various fixatives, including freeze-substitution and freeze-drying, but the results have always been consistent. In the fully epithelialized wound, when the epithelium has reverted to its normal thickness, glycogen is again detectable.

Staining the hypertrophic cells with toluidine blue to demonstrate cytoplasmic basophilia, which is indicative of RNA, shows the expected increase of this material in growing cells. In several instances the most intense cytoplasmic staining is in the perinuclear region (Fig. 4), which is

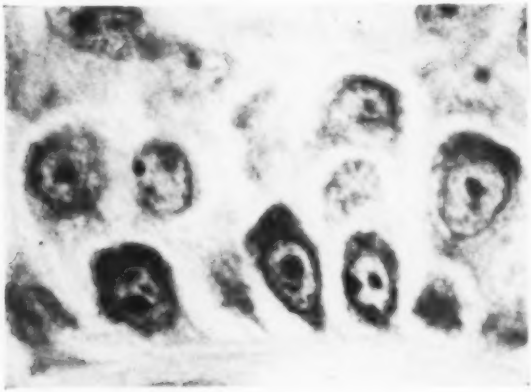

Fig. 4. Hypertrophic transitional epithelium, showing cytoplasmic basophilia that is particularly intense in the perinuclear region of some of the cells. Toluidine blue. (× 1230.)

in accord with the current theory that these proteins are synthesized in the first instance within nuclei in the region of the nucleoli, whence they migrate through the pores that are now known to exist in nuclear membranes into the perinuclear cytoplasm where they undergo further synthetic changes. The endoplasmic reticulum that can be identified with the electron microscope is the centre of protein production in the cytoplasm, and we are currently investigating the changes that may occur in this and other cell organelles in regenerating cells.

In the granulation tissue of the bladder wounds in the cat there is no alkaline phosphatase, and while this enzyme is normally present in transitional epithelium it largely disappears in migrating cells.

Thus in contrast to skin, bladder epithelium exhibits during repair a high degree of proliferative activity that includes mitosis in migrating cells and there would appear to be differences in carbohydrate metabolism as evidenced by the glycogen content of the two epithelia when regenerating.

Gall-bladder

When a small area of mucous membrane is removed from the gall-bladder of the cat, the repair proceeds in the usual manner with epithelial migration over a floor of accumulating granulation tissue. As in the urinary bladder, mitosis in normal gall-bladder epithelium is very rare, but within 24 hours of injury there is a very great increase, not only in marginal epithelium, but also in spreading cells as well (McMinn and Johnson, 1957). There can be very great changes in epithelial cell size and shape, ranging from a very flat, squamous form seen in the first 24 hours to the tall, hypertrophic variety found by the end of a week, by which time our lesions of 0.5 sq. cm. in area were fully epithelialized. Normal epithelial cells contain some perinuclear glycogen granules and have a PAS-positive border, but migrating cells show no such border. They continue to contain glycogen, although there does not appear to be such a dramatic accumulation as is found in epidermis. After complete epithelialization of the wound the PAS-positive border returns, and the glycogen content appears to return to the normal level. Alkaline phosphatase is always absent from the gall-bladder epithelium, is normally present in undisturbed subepithelial stroma, but as in other organs in the cat it is absent from granulation tissue.

Thus in the gall-bladder we have a further example of mitosis in migrating epithelium, but, in contrast to the urinary bladder, glycogen persists in the regenerating cells.

We can now pass on to consider lesions in the alimentary tract in a proper anatomical sequence.

Oesophagus

We have studied mucosal repair in the cat's oesophagus just above the cardia (McMinn and Johnson, 1958a). In the more superficial layers of hypertrophic and migrating epithelium, there is inflammatory infiltration and the formation of small spaces which give these layers a degenerative appearance, quite different from an epidermal wound and possibly due to the relatively septic environment of the oesophageal lesion. While at the margins there is increased mitotic activity in the epithelium, we have not observed mitosis in spreading cells, though this does not of course imply that it is not occurring. Granulation tissue accumulates in the usual way.

Glycogen is absent from normal epithelium, but in hypertrophic cells there is an accumulation such as is found in epidermis, and it disappears from new epithelium when the normal pattern has been restored following complete epithelialization. There is no apparent increase in cytoplasmic basophilia in regenerating cells, but this may be a dilution effect due to the comparatively large size of the cells. The alkaline phosphatase that has a characteristic distribution in the normal epithelium is not found in regenerating cells until complete epithelialization has occurred; as in other wounds in the cat, it is not present in the granulation tissue.

Thus in oesophageal epithelium during repair we have a pattern of hypertrophy, migration and carbohydrate metabolism similar to that in skin, but with a distinctive cellular infiltration of the upper epithelial layers.

Stomach

I include the stomach here simply to preserve the anatomical sequence, for our experiments on this viscus are still in progress and are by no means complete. A number of workers have shown that under favourable conditions mucosal lesions will heal with the formation of new glands. We have been supplementing our usual cytological methods with autoradiography, using sulphur 35 or tritium-labelled-thymidine in rats and cats. One example of each may be mentioned at this stage of our investi-

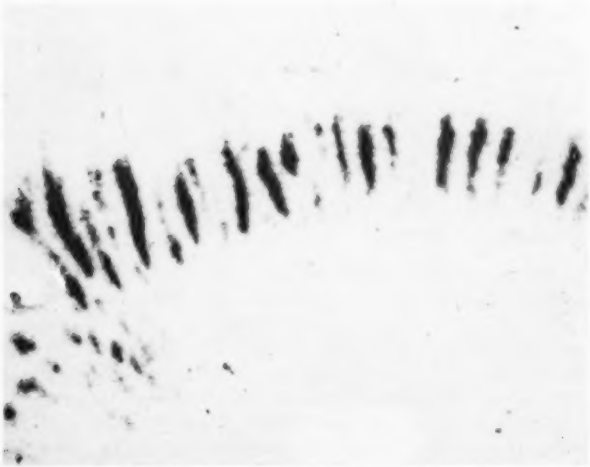

Fig. 5. Autoradiograph of the glandular part of the stomach of a rat injected with sulphur 35. Only the mucous neck cells normally show radioactivity (right), but as the wound margin is approached (left), many cells at deeper levels in the glands become capable of secreting sulphated mucin. (× 76.)

gations. Autoradiographs of the upper glandular part of the stomach of rats injected with sulphur 35 show that sulphated mucin is being produced by the mucous neck cells, and not by the surface epithelium or at deeper levels in the glands. However, at the margin of a mucosal lesion 5 days old, many more of the gland cells become mucus-producing (Fig. 5), but in the sheet of cells that migrates over the wound floor there is negligible radioactivity. The granulation tissue is strongly radioactive, due largely to the increased amount of sulphated mucopolysaccharide in the ground substance.

Thymidine is a substance that is incorporated into the DNA of cell nuclei and nowhere else in the body. If thymidine is labelled with the radioactive isotope of hydrogen H3 or tritium, it is possible to detect sites of DNA synthesis. Now it is well established that before a cell divides, the DNA content of its nucleus doubles in quantity so that the daughter nuclei may contain the normal amount. Thus using tritium-labelled-thymidine it is possible to detect cells that are about to divide, as evidenced by the pre-mitotic synthesis of DNA. Figure 6 shows an auto-

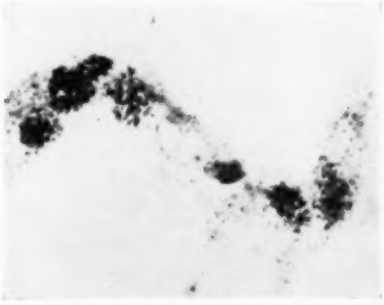

Fig. 6. Autoradiograph of migrating epithelium from a 5-day-old mucosal lesion in the stomach of a cat. Several nuclei are labelled with radioactive thymidine, indicating that they are in a pre-mitotic phase. Counterstained. (×740.)

radiograph of cells migrating from the margin of a 5-day old wound in the body of the cat's stomach, using a technique with this form of thymidine. The nuclei of several cells have incorporated the radioactive thymidine. With this abundant evidence of impending proliferation, it may be asked why mitosis in the spreading cells of gastric lesions has not been noted previously. The answer probably lies in examining, not random sections, but serial sections of the whole wound area, for the mitotic figures are there in ordinary material if one looks for them long enough (Fig. 7).

As I have mentioned, our gastric experiments are still in progress, but these autoradiographic techniques are already producing most interesting results.

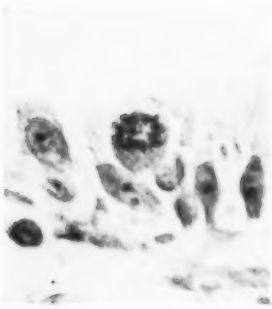

Fig. 7. Mitotic figure in a sheet of migrating epithelium from a 5-day-old gastric lesion in a cat. Van Gieson. (× 740.)

Small intestine

By way of introduction to intestinal lesions, I would like to remind you of the normal cyto-dynamics of this mucous membrane. In the intestinal glands (crypts of Lieberkühn) there is a high and constant degree of mitotic activity in the epithelial cells, and since cells are constantly being produced there must be an equivalent loss if equilibrium is to be maintained. By various methods including the use of mitotic inhibitors such as colchicine and of radioactive isotopes, it has been established that cells move upwards along the walls of the crypts (apparently sliding on the basement membrane) on to the sides of the villi, from the tips of which they are eventually shed. It has been calculated that in the rat the entire intestinal epithelium is renewed in approximately 1.5 days (Leblond and Stevens, 1948), and that in the cat the epithelium covering the villi is replaced in about 2.5 days (McMinn, 1954). A recent estimate for human duodenum suggests a renewal period similar to the rat of about 1.5 days (Bertalanffy and Nagy, 1958). This is an enormous rate of cell turnover. It has been said concerning the vast number of red blood cells that are manufactured and destroyed every day that " the formation and removal of this number of living cells per day in such a manner as to preclude any mistakes must occur with a mathematical precision resembling the motion of the planets about the sun " (Hoffman, 1953). It seems that the constant renewal of intestinal epithelium is a no less remarkable phenomenon.

With regard to mucosal lesions in the intestine, under favourable conditions new crypts and villi are formed. Florey and Harding (1935) noted this in the cat's duodenum, and our own experiments on the ileum confirm it (McMinn and Mitchell, 1954). For the first 24 hours or so the migrating epithelial cells have a very flattened appearance (Fig. 8) and we are currently studying with the electron microscope the changes that occur

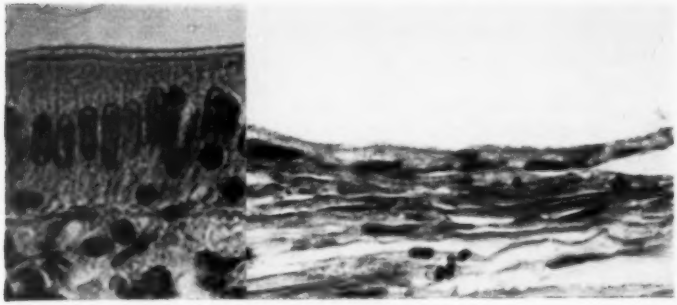

Fig. 8. Normal intestinal epithelium from a cat (left), for comparison with migrating cells from a lesion in the ileum after 24 hours, at the same magnification. H. and E. (× 760.)

in cell contact during the early stages of repair. Normally, the boundary membranes of adjacent cells interlock with one another, rather like the parietal bones in the sagittal suture of the skull, and it would be interesting to know how this interlocking mechanism becomes modified during migration.

By the end of 2 weeks the precursors of new crypts and villi are very evident at the wound margins, and after 6 weeks an original wound area 0.5–1.0 sq. cm. in size is covered by irregular villous-like projections which by the end of 6 months very closely resemble normal villi. As in all other regions of the alimentary tract, the muscularis mucosae never regenerates.

In our original study on the ileum, Mitchell and I counted a total of over 100,000 epithelial cells at the margins of these artificial mucosal lesions at various stages of healing, using colchicine, in order to compare the number of mitotic figures at wound margins with the normal degree of crypt activity (McMinn and Mitchell, 1954). The results were interesting in that, contrary to the visual impression, on statistical analysis there was no significant increase in the amount of mitotic activity at wound margins compared with that in normal crypts. The small intestine thus appears to be an exception to the general rule of increased epithelial proliferation during repair. It seems to be a matter of indifference to crypt cells whether their daughters pass along the side of a villus or over the floor of a lesion. Recently, however, we have noted very occasional mitotic figures in migrating cells in lesions of both the small and large intestines.

Large intestine

Experimental wounds of rectal mucosa in the cat begin to heal in the familiar manner with epithelial migration and the formation of granu-

lation tissue. After the first week or so, the subsequent mode of repair in the cat seems to be rather different from the constant pattern of new gland formation noted at higher levels of the alimentary tract such as the stomach, duodenum and ileum. In the rectum there seems to be a variation depending on whether there is a minimal or an excessive accumulation of granulation tissue (McMinn and Johnson, 1958b). Where it is excessive, epithelium fails to cover the mound of granulation and the subsequent histological picture gives an impression of contraction simply drawing the edges of the mucosa together. This is what O'Connor (1954, 1956) found to occur regularly in the colon and rectum of the mouse, resulting after some weeks in the formation of a well marked fibrous tissue septum at the wound site. In contrast, some of our specimens from the cat show no excess of granulation tissue, and in these, epithelial depressions seem to presage the formation of new glands, the end result being new crypts covering the whole wound area. The fact that new crypts can occur at least in some specimens is supported by histochemical evidence. Normal rectal epithelial cells in the cat possess a striated border giving a strong reaction for alkaline phosphatase, and cytoplasm that does not contain glycogen. Migrating epithelial cells do not show a phosphatase-positive border, and by the end of the first week perinuclear glycogen granules can be detected in the cytoplasm. Thus migrating epithelial cells are characterized by the absence of phosphatase and the presence of glycogen. Now the cells lining the epithelial depressions that seem to be the precursors of new crypts possess just these characteristics, so that these depressions appear to be newly forming crypts rather than merely old crypts that perhaps could have become distorted by contraction.

DISCUSSION

In summarizing these results, I would like to mention epithelium first and then connective tissue, though this is not to dissociate the influence that one may have on the other. As in embryological growth, so during repair there must be considerable interplay between new epithelium and new connective tissue, such as in the formation of new gastric and intestinal glands, and in skin the possible importance of these interactions in grafting and in the pathogenesis of neoplasia has been stressed by Gillman *et al.* (1955a).

There seems to be little doubt that the new epithelial cells in our studies have been derived from their respective parent epithelia. There have been in the past occasional reports of metaplasia of connective tissue cells, in the uterus, skin and stomach, and, while there does not appear to have been a great deal of sympathy for these views, Willis (1958) has recently stressed the need for further studies of stromal metaplasia in epithelia. However, in mesothelial surfaces such as peritoneum and synovial membranes there

seems no doubt that metaplasia does play a part in the restoration of surface continuity both in animals and in man (Brunschwig and Robbins, 1954; Levene, 1957).

We have seen during the first 24 hours or so of repair in most epithelia the appearance of a very flattened form of cell that is never seen at later stages. We cannot be certain whether such cells die and disappear or whether they revert to a more normal shape, but they may be compared with the large flat cells that Poole *et al.* (1958) found during the regeneration of aortic endothelium. Contrary to some previous reports, these workers noted that new endothelial cells arose by mitotic division, and that at the edge of the slowly advancing sheet, many cells of giant size were found which persisted for months and possibly indefinitely. It would be interesting to know the reason for the persistence of these abnormal endothelial cells in comparison with the disappearance of such forms in epithelia.

A notable feature of our studies has been the occurrence of mitosis in migrating epithelial cells. It is frequently stated that cells in migrating sheets do not divide, but in view of our findings this generalization is no longer tenable, although the possible significance of this has yet to be shown. It may well be that mitosis in migrating epithelium is of universal occurrence, and although we did not see any evidence of this in the oesophagus we have probably not looked at a sufficient number of sections, as witness past experience with gastric lesions compared with our thymidine results. We fully endorse the need for examining serial sections, as stressed by Gillman and Penn (1956), and agree with the suggestion of Edwards and Dunphy (1958) that many authors in the past have erroneously minimized the role of mitosis during epithelial repair. The recent observations of Weiss and Matoltsy (1959) have some bearing on this matter. They found that in skin wounds made in chick embryos before the tenth day there was considerable mitotic activity resulting in the heaping up of epithelial cells at the margins, but there was no migration except in wounds made after the tenth day. The discovery of the reason for this, which may possibly be hormonal, may help considerably in our understanding of the relationship between migration and mitosis. Quite apart from the factors that initiate these processes, we are ignorant of the mechanisms that cause their cessation when a defect has been re-covered by epithelium, and there is much to be learnt in this particular field.

With regard to carbohydrate metabolism in regenerating epithelium, it seems from our studies that there is no universal pattern as evidenced by glycogen accumulation. None of the theories so far advanced to explain this phenomenon is entirely acceptable (Scothorne and Scothorne, 1953), and further progress in this matter probably requires studies of a biochemical rather than a histochemical nature. The possibility that histo-

chemical tests do not tell the whole glycogen story is emphasized by the current work of Kugler and Wilkinson (1959). Glycogen in cells exists in two forms—one a protein-bound fraction, and the other a fraction that is soluble in trichloracetic acid, the TCA fraction. Kugler and Wilkinson have claimed that the usual histochemical tests reveal only the TCA-soluble fraction, and that considerable quantities of protein-bound glycogen may exist in cells and remain undetected histochemically. The reasons for a change from one fraction into another are unknown, but this could be a possible explanation for the rather variable histochemical results, although there is no reason for supposing that all epithelia, with their diverse functions, should behave similarly.

As far as connective tissue is concerned, I have said nothing about the important problem of contraction, which contributes to the closure of all wounds. In skin, the work of Abercrombie *et al.* (1956) has shown that it is not the fibres but the cells of new connective tissue that are responsible, and van den Brenk (1956) has emphasized that there is an essential difference between contraction in the early stages of repair and later cicatrization. While a number of workers seem to be studying contraction in skin, contraction in visceral wounds is still virgin territory.

The formation of the extracellular components of connective tissue cannot take place without the presence of the cells commonly known as fibroblasts, but there is as yet no certainty concerning the precise origin of these cells. In a current review Johnson and I (1960) have mentioned some opinions on this matter and, without going into details here, there is the possibility, as cited by Gillman *et al.* (1955b), that these fibroblasts are not derived from pre-existing fibrocytes but arise by metaplasia of blood cells that have immigrated into the area. This is a concept that is not new but is of great importance, not only from the point of view of tissue repair, but also in the understanding of the general role in the body of such cells as lymphocytes and reticulo-endothelial cells. This is another field that must be intensively explored.

Some of the histochemical changes in granulation tissue have been summarized recently by Dunphy and Udupa (1955), and I will here refer only to the role of alkaline phosphatase. The original observations on the association of phosphatase with new fibrous tissue formation were made by Fell and Danielli (1943) in rodents, and while a number of subsequent workers have confirmed their observations others have not been able to do so. Despite the fact that Danielli *et al.* (1945) queried whether species differences might exist, general statements appear from time to time maintaining that new fibroblasts contain phosphatase. In the light of our findings in the cat this is no longer true, although the little information so far available from human subjects, from skin wounds (Fisher and Glick, 1947) and gastric ulcers (Fodden, 1953), suggests that phosphatase is

present. However, while the biochemist can tell us precisely what the enzyme can do chemically, the reason for its presence in many body sites is not known, and even its apparent role in, for example, absorption from the gut is by no means proven.

From the little I have been able to tell you about repair in mucous membranes, it is clear that we are still merely paddling on the edge of the wound healing ocean, but I believe that by experiment and by the application of techniques such as I have described we shall eventually learn more and more of what Young (1956) has called " the organization of cellular events " during repair. The speeding up of growth and differentiation that occurs in repair may also help in the understanding of growth and differentiation during embryological development, for one is often a reflection in whole or in part of the other. Our own particular purpose for the future, now that we have a certain amount of experimental background, is to apply these techniques to human material such as peptic and varicose ulcers, in order to investigate, for example, the precise cytological changes at the margins of acute and chronic lesions, as one step in determining why the former heal readily while the latter do not. The late Evarts Graham wrote in 1955: " Some day we shall know more about the fundamental chemical factors involved in the healing of a wound—about the enzymes that construct fibrous tissue from the fibroblasts and that stimulate the epithelium of the skin and mucous membranes to cover the fibrous tissue and then stop growing ". When that day comes, medicine will have made a considerable advance. And I use the word medicine, Mr. President, in its very widest connotation, bearing in mind that I have had the honour to address you in this famous centre of surgical learning.

FURTHER ACKNOWLEDGMENTS

I would like to express my gratitude to Professor Francis Davies for his constant encouragement and for the facilities provided in his Department in the University of Sheffield. I would also like to acknowledge the photographic skill of Mr. J. H. Kugler, and the technical assistance of Mr. J. H. Morrill, Mr. D. A. Allen and Miss C. J. Crockford.

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FACULTY OF DENTAL SURGERY

AT A MEETING of the Board of Faculty on 18th March, the Board learned with regret of the death of Mrs. Lilian Lindsay, C.B.E., F.D.S.R.C.S., who had recently been awarded the Colyer Gold Medal for her outstanding contributions to dentistry.

At the same meeting, Dr. B. Orban, of Chicago, was appointed Webb-Johnson Lecturer for the period 1958–1961. It is hoped that Dr. Orban will deliver his lecture in September of this year.

PRESENTATION OF THE HONORARY MEDAL OF THE COLLEGE AND ADMISSION TO THE FELLOWSHIP

AT THE MEETING of Council on 10th March, the Honorary Medal of the College was presented to Sir Cecil Wakeley, Bt., K.B.E., C.B., LL.D., F.R.C.S., Past President of the College.

The President presenting the Honorary Medal of the College to Sir Cecil Wakeley, Bt., with Mr. A. Dickson Wright, Senior Vice-President, in the centre of the picture.

The President, Professor Sir James Paterson Ross, Bt., K.C.V.O., addressed Sir Cecil thus:

"Sir Cecil Wakeley, I am sure that everybody here present is delighted to welcome you to this meeting of the Council to receive the Honorary Medal of the College, and I think that in case you have not already seen it, I should read to you the resolution of the Council, passed at the last meeting—that the Medal should be presented to you, Sir, in recognition of your distinguished labours on behalf of the College over a long period, including five years as President, a tribute to your success as Editor of the Annals, and the untiring and vigorous devotion to the affairs of the College and the remarkable aura of friendliness which distinguishes all your endeavours.

"I think we must remind ourselves that your association with the College must date back almost fifty years to your student days. You have been a member of the Court of Examiners, both for the Primary and for the Final Fellowship, and Member of Council and, as is stated in the minute, its President for five years. As a Lecturer, I think you were five times a Hunterian Professor, the Hunterian Orator, Bradshaw Lecturer and Vicary Lecturer. Your association with our kindred body, the Imperial Cancer Research Fund—and particularly now as its Chairman—is of the greatest value to us in this College and we are glad that recently you have consented to become a Hunterian Trustee. Therefore it is not too much to say that your whole life has been identified with the affairs of the College, and I am sure it is right that the Council should have decided to award you this Honorary Medal which I have very much pleasure in presenting to you now, together with this document, which has on it the names of all the present members of the Council. I am sure that every one of them must be pleased, as each one of us here has experienced that aura of friendliness. I personally feel very grateful to you for many kindnesses and I am sure that that applies to most of my colleagues."

Sir Cecil, replying, said:

"Mr. President, Members of Council:

"You have today done me great honour and I am very pleased indeed and wish to thank you all very much. When I consider the great personages who have had this great distinction bestowed upon them in the past, I am very mindful of my own shortcomings. The great names of men who have received this honour in the past come back to me—James Paget, Lord Lister, Alexander Fleming, Lord Webb-Johnson and Frederic Wood Jones, to mention but a few. These men in their time gave great service to this College and have made its name ever more famous.

"You are right, Sir, when you say that I first became associated with this College in my student days, fifty years ago, when I came here to seek help from Sir Arthur Keith on an anatomical problem. Sir Arthur Keith was always willing to do his best to help anyone who came to seek advice about any difficult problem. During the last fifty years, vast changes have indeed taken place in this College and it has blossomed forth from a mere dull mausoleum of skulls and skeletons to a great institution in which the research and teaching taking place must be the pride of all Fellows of the College.

"You, during your Presidency, Sir, have added lustre to the College and the College itself has gone from strength to strength, and I am sure this augurs well for the future and that those who come here will recognize what the College has meant to surgery.

"I would like to thank you, Sir, for your very kind words, and I would like to say on behalf of my wife and myself how much pleasure it has given us to come here today."

Miss I. Forshall, Mr. P. G. C. Martin, Mr. G. E. Moloney and Professor A. W. Kay, who had previously been elected to the Fellowship *ad eundem*, were formally admitted, and, after each new Fellow had signed the Roll, the President addressed them as follows:

"In welcoming you all today, I think we should realize that the honour of the Fellowship *ad eundem* is something which the Council bestows discreetly and sparingly. It is something which we hope will give you all the feeling that you are very welcome as Fellows of Colleges in other countries working in this country and, although I am sure that because of your distinction in the profession and your personal attributes you are already thoroughly established and welcome in your own neighbourhoods, I would like you to feel, and the Council would like you to feel, that you now have a right to come to this College as Fellows, because we want you to feel that being in England you have the Fellowship of the Royal College of Surgeons of England as well as that of your own original College, and therefore we welcome you very warmly and are very glad to be able to admit you today."

The President addressing the new Fellows *ad eundem*. *Left to right:* The President, Mr. A. Dickson Wright (Senior Vice-President), Professor A. W. Kay, Mr. G. E. Moloney, Mr. P. G. G. Martin, Miss I. Forshall, Mr. Lawrence Abel, and Sir Stanford Cade, K.B.E., C.B. (Junior Vice-President).

In reply, Miss Forshall said:

" Mr. President, Members of Council:

" I wish to thank you for the honour that you have done to Mr. Martin, Mr. Moloney, Professor Kay and myself. I want to thank you, not only for ourselves, but for the postgraduate schools of London, Oxford, Sheffield and Liverpool who will, because of our working in these places, be most grateful for the honour that has been done us. I would like very much indeed to thank the President for the very kind words he has spoken to us, and we have already tasted the hospitality of the College and for this, too, we wish to thank you all."

APPOINTMENT OF FELLOWS AND MEMBERS TO CONSULTANT POSTS

A. SINHA, F.R.C.S. — Associate Professor in Otolaryngology at the All-India Institute of Medical Sciences, New Delhi.

The Editor is always glad to receive details of new appointments obtained by Fellows and Members, either through the Hospital Boards or direct.

PROCEEDINGS OF THE COUNCIL IN MARCH

AT A MEETING of the Council on 10th March 1960, with Professor Sir James Paterson Ross, Bt., President, in the Chair, the Honorary Medal of the College was presented to Sir Cecil Wakeley, Bt., Past President, in recognition of his distinguished labours for the College.

Miss I. Forshall, Mr. P. G. C. Martin, Mr. G. E. Moloney and Professor A. W. Kay, who had previously been elected *ad eundem* to the Fellowship, were formally admitted.

The Hallett Prize was presented to John Coundley Doyle of the University of Melbourne, and Handcock Prizes to S. J. McDonald (Charing Cross) and D. R. Harvey (Guy's).

Licences in Dental Surgery were granted to 76 candidates.

One Diploma of Fellowship in the Faculty of Anaesthetists was granted.

The twenty-ninth Macloghlin Scholarship was awarded to A. S. Coulson of Hendon Grammar School.

The following hospitals were recognized under paragraph 23 of the Fellowship Regulations:

Hospitals	Posts Recognized		
	General (6 months unless otherwise stated)	Casualty (all 6 months)	Unspecified (all 6 months)
LIVERPOOL — Alder Hey Hospital and Broadgreen Hospital (additional)			*Under para.* 23 (c) Registrar (Otorhinolaryngology)
HERTFORD — County Hospital (confirmation of temporary recognition)		Casualty Officer	
CHESTER — Royal Infirmary (additional)		Casualty Officer	
LONDON — Queen Mary's Hospital (Roehampton) (additional)			S.H.O. (Orthopaedics)
EPPING — St. Margaret's Hospital (additional)	H.S. 2nd Surg. Reg. post to be recognized for 12 instead of 6 months.		
SCARBOROUGH — Hospital (additional)	Surg. Reg.		
NORTHAMPTON—General Hospital (additional and redesignation)			Registrar (Orth. and Fracture) *Under para.* 23 (c) House Officer redesignated as S.H.O.
BARNET — General Hospital (redesignation)		S.H.O. 6 months Casualty	S.H.O. 6 months Orthopaedic

SWINDON —Transfer of recognition (2 Resident Casualty Officers) from the Great Western Hospital to the new Princess Margaret Hospital (for periods of six months' casualty training).

DONATIONS

DURING THE LAST few weeks the following generous donations have been received:

Appeal Fund—Donations:

£5,000	Finnamore Trustees (for Mr. Basil Mavroleon).
£1,322	Cyanamid of New York
£250	The Stock Exchange
	Rowe & Pitman
	Whitehall Securities Corporation Ltd.
£200	Panmure, Gordon & Co.
£105	George Jowitt & Sons, Ltd.
	L. Messel & Co.
£100	Greenfriar Investment Co. Ltd.
	The Witan Investment Co. Ltd.
	Edward Pryor & Son, Ltd.
	George Henderson & Co.
£78 15s. 0d.	Myers & Co.
£52 10s. 0d.	Turriff Construction Corporation Ltd.
	Montagu, Loebl, Stanley & Co.
	Newton Chambers & Co. Ltd.
£50	Pidgeon & Stebbing
	E. A. Grey, Esq.
£31 10s. 0d.	Tottenham Group Hospital Management Committee.
£26 5s. 0d.	The Worshipful Society of Apothecaries of London.
	McCall & Co. (Sheffield), Ltd.
£25	James Capel & Co.
	Higher Speed Metals, Ltd.
	D. F. Hellings, Esq.
£21	George H. Cook & Co. Ltd.
	W. L. Marrison, Ltd.
£10 10s. 0d.	A. G. Burrell & Co. Ltd.
	Fenn & Crosthwaite
	Ernest H. Hill, Ltd.
	A. W. Peake, Esq.
	Richard Lunt & Co. Ltd.
	Pickford, Holland & Co. Ltd.
	Mrs. B. C. Bervon
£10	Mrs. M. Vigar
£5 15s. 0d.	Mrs. M. Jones
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£5	Blackwell & Co.
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£3 8s. 0d.	Miss E. Williams
£3 3s. 0d.	Miss E. M. Callow
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£2 2s. 0d.	Joseph Peck, Ltd.
	Wissmann & Co.
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	G. W. Ford & Son, Ltd.
£2	Y. Bissell, Esq.
£1 1s. 0d.	Plant & Sons, Ltd.
	A. J. Drury, Esq.
10s. 0d.	G. M. Crocker, Esq.

DONATIONS

Appeal Fund—Covenants:

£3,000 p.a. for 7 years	Prudential Assurance Co. Ltd.
£500 p.a. for 7 years	Bowater Paper Corporation Ltd.
£233 9s. 5d. p.a. for 7 years	Edgar Allen & Co. Ltd.
£100 p.a. for 7 years	Arnold Laver & Co. Ltd.
£75 p.a. for 7 years	Wrensons Stores, Ltd.
£26 5s. 0d. p.a. for 7 years + tax	Ridge Limestone, Ltd.
	Withers Limestone, Ltd.
	Holme Park Lime, Ltd.
	Thomas Black, Ltd.
	Industrial Plant (Combustion), Ltd.
£8 3s. 3d. p.a.	James Neill & Co.

Restoration and Development Fund:

£25	Faculty of Radiologists
£21 3s. 0d.	Association of Anaesthetists of Great Britain and Ireland

Voluntary annual subscriptions and donations by Fellows and Members:

The following Fellows and Members of the College, Fellows in Dental Surgery and Fellows in the Faculty of Anaesthetists have generously given donations or have undertaken to make a voluntary annual subscription under Covenant to the College:

J. T. Anderson, F.F.A.R.C.S.
A. Barnsley, F.F.A.R.C.S.
M. Birnstingl, F.R.C.S.
F. K. Boston, F.F.A.R.C.S.
T. J. Butler, M.D., F.R.C.S.
W. E. Earle, M.R.C.S., L.D.S.R.C.S.
P. F. Early, F.R.C.S.
M. W. Goldsmith, F.F.A.R.C.S.
G. E. Hale Enderby, F.F.A.R.C.S.
Prof. G. E. M. Hallett, F.D.S.R.C.S.
C. R. Helsby, F.R.C.S.
J. C. Hewitt, F.F.A.R.C.S.
Miss G. Hill, F.R.C.S.
A. Hulme, F.R.C.S.
G. S. A. Knowles, F.F.A.R.C.S.
Miss E. Landau, F.F.A.R.C.S.
W. S. McConnell, F.F.A.R.C.S.
V. O. McCormick, F.F.A.R.C.S.
G. G. Macphee, F.D.S.R.C.S.
P. J. W. Monks, F.R.C.S.
A. H. Musgrove, F.F.A.R.C.S.
M. D. Nosworthy, F.F.A.R.C.S.
W. E. Quitman, F.F.A.R.C.S.
W. K. Rae, F.F.A.R.C.S.
C. G. Sinclair, F.R.C.S.
W. E. Tucker, C.V.O., M.B.E., T.D., [F.R.C.S.
J. R. M. Whigham, F.R.C.S.
J. F. R. Withycombe, F.R.C.S.

RECENT OVERSEAS VISITORS TO THE COLLEGE

RECENT OVERSEAS VISITORS to the College have included Professor Fernand Orban, O.B.E., who delivered a Moynihan Lecture in the College in March, and Madame Orban; and Mr. Howard Eddey, F.R.C.S., F.R.A.C.S., of the University of Melbourne, who delivered a Hunterian Lecture, and Dr. K. J. Grice, also of the University of Melbourne.

ANATOMICAL MUSEUM

THE SPECIAL DISPLAY for the month of April consists of a further selection of Quekett's microscopical preparations.

NEW COLLEGE PUBLICATIONS

Readers are reminded that two new publications are now available and may be ordered from the Librarian of the College or from any bookseller.

The History of the Royal College of Surgeons of England

The official history of the College, written by Sir Zachary Cope, F.R.C.S., and published by Anthony Blond, Ltd. Price 63s. a copy, postage 2s. The author has traced the development of the College from a City Livery Company to the progressive surgical institution that it is at the present time. There are biographies of distinguished surgeons and the volume is illustrated with more than 36 pages of plates. The Librarian has contributed a chapter on The Library, and Miss Jessie Dobson has written the history of the Hunterian Museum.

A New Catalogue of Portraits, price 30s. a copy, postage 1s. 3d. This new catalogue has been compiled by the Librarian of the College, Mr. W. R. Le Fanu, M.A., and contains descriptions of all the portraits and paintings in the College with details of their history. There are four coloured plates and over 100 black-and-white illustrations. Published by Messrs. E. & S. Livingstone.

BINDING OF THE ANNALS

BINDING CASES ARE not provided for completed volumes of the ANNALS but the Editor can recommend the firm of Lovett, Bookbinders, 86, Plashet Grove, London, E.6, who will undertake the binding in buckram or leather to individual requirements at reasonable prices.

DIARY FOR APRIL

Tues.	19		Last day for nomination of candidates for the Council.
Wed.	20		Second L.D.S. Examination begins.
Thur.	21	4.15	DR. B. D. WYKE—Arnott Demonstration—The human cerebral circulation.
Fri.	22		Surgical Lectures and Clinical Conferences end.
		5.00	PROF. K. BLOOR—Hunterian Lecture—Natural history of arteriosclerosis of the lower extremity.
Sat.	23		Last day for applications for Lectureships.

Tues.	26		Final Fellowship Examination (Ophthalmology and Otolaryngology begins.
			Lectures and Clinical Demonstrations in Dental Surgery begin.
		5.00	MR. T. WARD—Fractures of the facial bones—I.
		6.15	MR. P. W. CLARKSON—Surgical correction of deformities of the jaws.
Wed.	27	5.00	DR. A. A. BARTON—Arnott Demonstration—Wings.
Thur.	28	5.00	PROF. W. J. METCALFE—Hunterian Lecture—Arterial embolism in the lower limbs.
		5.00	MR. G. T. HANKEY—Disorders of the mandibular joint.
		6.15	MR. B. W. FICKLING—The maxillary antrum in relation to dental surgery.
Fri.	29		Names of candidates (F.D.S.) for election to the Board of Faculty of Dental Surgery announced and voting papers issued.

DIARY FOR MAY

Tues.	3		Date of election of Licentiate to the Board of Faculty of Dental Surgery announced.
			Final Fellowship Examination (General Surgery) begins.
		5.00	DR. J. R. B. WILLIAMS—Erasmus Wilson Demonstration.
		5.00	SIR STANFORD CADE, K.B.E., C.B.—Malignant tumours of the jaws.
		6.15	MR. I. R. H. KRAMER—Pulp reactions to operative procedures.
Thur.	5		D. Path. Examination begins.
		5.00	MR. J. WATSON—Head Injuries.
		5.30	SIR VICTOR NEGUS—Otolaryngology Lecture.
		6.15	DR. B. COHEN—Secondary tumours of the jaws.
Fri.	6		Voting papers for Council issued.
			Basic Sciences Lectures and Demonstrations end.
Tues.	10	5.00	DR. L. FORMAN—Oral manifestations of skin diseases—I.
		6.15	MR. N. L. ROWE—Odontogenic and developmental cysts of the jaws.
Thur.	12		D.A. Examination begins.
		2.00	Ordinary Council.
		5.00	PROF. N. C. TANNER—Hunterian Lecture—Technique and late results of porto-azygos disconnexion for oesophageal varices.
		5.00	DR. L. FORMAN—Oral manifestations of skin diseases—II.
		6.15	PROF. H. C. KILLEY—Soft tissue infections of the face and neck.
Tues.	17	5.00	DR. W. CAMPBELL—Radiology of the facial bones—I.
		6.15	PROF. R. B. LUCAS—Pathology of oral neoplasms—I.
Thur.	19	5.00	DR. W. CAMPBELL—Radiology of the facial bones—II.
		6.15	PROF. R. B. LUCAS—Pathology of oral neoplasms—II.
Fri.	20	5.00	Board of Faculty of Dental Surgery.
Tues.	24		Last day for nomination of candidates (L.D.S.) for election to the Board of Faculty of Dental Surgery.
		5.00	MR. B. E. D. COOKE—Fibro-osseous swelling of the jaws—I.
		6.15	DR. M. J. F. MCARDLE—Facial pain.
Wed.	25		Primary Fellowship Examination begins.
Thur.	26	5.00	MR. B. E. D. COOKE—Fibro-osseous swelling of the jaws—II.
		6.15	MR. C. R. MCLAUGHLIN—Cleft palate.
Tues.	31	5.00	DR. W. S. MCCONNELL—General Anaesthesia—I.
		6.15	MR. S. H. WASS—Osteomyelitis of the jaws.

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[1]Rutter, A. G., *Lancet*, 1959, **i**, 1173.
[2]Ganz, P., and Zindler, S., *Medizinische*, 1955, **29-30**, 1042.

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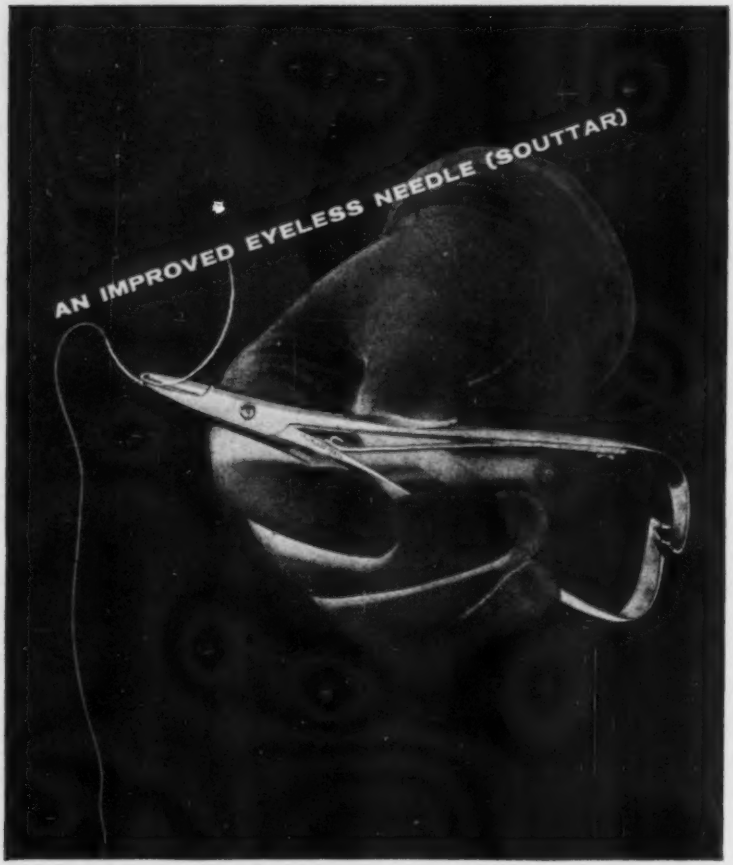

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